FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE (DODAC)

Friday, October 13, 2017

8:30 a.m. to 1:23 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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Division of Advisory Committee and

Consultant Management

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. CHODOSH: Good morning. I'm working from a script. I'll try not to make it sound like it.

My name is James Chodosh. I first need to remind everybody to silence your cell phones, smartphones, and any other devices that might make sound during the meeting, and I also need to identify the FDA press contact, Theresa Eisenman, who I don't believe has arrived at this point.

Again, I'm James Chodosh. I'm chairing this meeting of the Dermatologic and Ophthalmologic Drugs Advisory Committee, and I'm calling the meeting to order as of now. We're going to start by going around the table and introducing ourselves, and if we could start with you, John.

DR. FARLEY: Good morning. I'm John Farley. I'm deputy director of the Office of Antimicrobial Drug Products in which the Division of Transplant

and Ophthalmology Products resides at CDER, FDA.

DR. CHAMBERS: Good morning. I'm Wiley Chambers. I'm a supervisory medical officer in the Division of Transplant and Ophthalmology Products.

DR. WADHWA: Good morning. I'm Sonal Wadhwa. I'm a medical officer in the Division of Ophthalmology and Transplant Products.

DR. DENG: Good morning. My name is Yunfan Deng. I'm the statistical reviewer in the Division of Biometrics in the Office of Biostatistics.

DR. EMERSON: I'm Geoff Emerson. I'm an ophthalmologist in Minneapolis.

DR. KWON: Good morning. My name is Young Kwon. I'm a professor of ophthalmology specializing in glaucoma at University of Iowa.

DR. OLIVIER: Mildred Olivier from Chicago, Illinois and glaucoma specialist professor at Rosalind Franklin University.

CDR BONNER: Good morning. My name is LaToya Bonner. I'm the DFO for DODAC.

DR. ZLOTY: Peter Zloty, ophthalmologist, Mobile, Alabama.

DR. HAWKINS: Good morning. Randy Hawkins, internal medicine and pulmonary medicine in Los Angeles, California and member of the Medical Board of California.

MS. DeLUCA: Jo Ellen DeLuca. I'm the patient representative.

DR. KING: Good morning. I'm Tonya King, professor of biostatistics at Penn State College of Medicine.

DR. GICHERU: Sid Gicheru, I'm an ophthalmologist in private practice from Dallas, Texas.

DR. YOO: Good Morning. Dave Yoo. I am an ophthalmologist associate professor at Loyola in the Chicago area specializing in oculoplastics.

DR. SULTAN: Morning. Marla Sultan, ophthalmologist working at Pfizer as a global clinical lead in global product development, serving as the industry representative.

DR. CHODOSH: Thank you so much.

For topics such as those being discussed at today's meeting, there are often a variety of

opinions, some of which are strongly held. Our goal is we have a fair and open forum for discussion of these issues and that individuals with interest can express their views without interruption.

As a general reminder, I would tell you that individuals will be allowed to speak into the record only if recognized by the chair -- that's me -- and we're looking forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the 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 may be anxious to speak with FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the

meeting topic during breaks or lunch. Thank you.

I'm going to pass it on to Commander LaToya Bonner, who will read you the conflict of interest statement.

Conflict of Interest Statement

CDR BONNER: The Food and Drug Administration is convening today's meeting of the Dermatologic and Ophthalmologic 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 conflicts of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, 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 special government employee's services outweighs his or her potential financial conflict of interest, or when the interests of a federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions 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; consulting; expert witness testimony; contracts, grants,

CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of the safety and efficacy of new drug application 208254 for netarsudil ophthalmic solution 0.02 percent submitted by Aerie Pharmaceuticals, Incorporated for the proposed indication to reduce elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. This is a particular matters meeting during which specific matters related to Aerie's NDA 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. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Marla Sultan is participating in this meeting

as a nonvoting industry representative acting on behalf of regulated industry. Dr. Sultan's role at this meeting is to represent industry in general and not any particular company. Dr. Sultan is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. CHODOSH: Thank you so much.

We're now going to proceed with the FDA introductory remarks, and I present Dr. Wiley Chambers.

FDA Opening Remarks - Wiley Chambers

DR. CHAMBERS: Thank you very much and good

morning. Welcome on behalf of the FDA, including the Center for Drug Evaluation and Research, the Office of Antimicrobial Drug Products, and the Division of Transplant and Ophthalmology Products.

Today FDA is asking the advisory committee to discuss netarsudil ophthalmic solution, which is proposed to lower intraocular pressure in individuals with elevated intraocular pressure or glaucoma. While there remain no available cures for glaucoma, the proposed claim for this product, similar to other products, is to deal with one of the leading risk factors, elevated intraocular pressure, which we know contributes to potential blindness.

We continue to be encouraged by the development of products that attempt to make glaucoma manageable. While the FDA does not routinely bring all new drug applications to an advisory committee for discussion, we specifically consider whether every new molecular entity would benefit from discussion at an advisory committee meeting. In this particular case, the fact that

netarsudil is a new class of drug products has prompted us to bring the clinical portion of this application for committee discussion.

I would like to remind everybody that we only intend to discuss the clinical aspects of this application. As part of the review of this application and prior to any approval, the nonclinical studies, the identity, purity, quality, sterility, stability, manufacturing, and storage facilities will also be reviewed by FDA staff. Today we're only discussing the clinical portion.

I want to sincerely thank all the members of this committee who have given their time in order to participate in today's discussion. I also want to thank members of the FDA review team, the advisory committee staff who have all worked hard to prepare for this meeting, as well as the company who is presenting the product. Thank you very much.

DR. CHODOSH: Thank you, Wiley.

Both the Food and Drug Administration and the public believe in a transparent process for

information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the applicant's nonemployee presenters, to advise the committee of any financial relationships that they may have with the applicant, such as consulting fees; travel expenses; honoraria; and interests in the sponsor, including equity interests and those based on the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We are now going to proceed with the Aerie Pharmaceuticals presentations, which will be

limited to one hour, please.

Applicant Presentation - Marvin Garrett

MR. GARRETT: Good morning, Mr. Chairman, members of the committee, and our colleagues from FDA. My name is Marvin Garrett. I'm the vice president of regulatory affairs and quality for Aerie Pharmaceutical.

Aerie was founded in 2005 as a spinout from Duke University. After years of research, we find ourselves filing an NDA February of 2017, and we're here today to discuss the safety and the efficacy of a new molecular entity, first in class for lowering intraocular pressure.

We respectfully request, after reviewing our safety and efficacy data, that we would hope we get a recommendation for approval for our new drug, netarsudil ophthalmic solution 0.02 percent for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension to be dosed one drop once a day.

The program is as follows. In the interest of time, I won't introduce each speaker. They will

announce themselves with proper disclosure at the beginning of each presentation.

In addition to those listed here as presenters, we have, in the box, a group of expert responders that will take any of your questions. We welcome a vigorous discussion, and we will entertain any of your questions.

With that, I'd like to hand it over to Rick Lewis.

Applicant Presentation– Rick Lewis

DR. LEWIS: Thank you, Marv, and good morning, everyone. I'm the chief medical officer for Aerie, also a practicing ophthalmologist specializing in glaucoma in California.

This is an exciting time in glaucoma. We've had a lot of innovation happening. It's also a period that having practiced 35 years, it's a bit of a frustrating time because innovation has been slow in the therapeutic area for treating our patients.

It's been an exciting time for me to be part of the development of this product, netarsudil.

And in the 10 minutes allocated allocated to unmet needs, I'm going to go over the prevalence and diagnosis of glaucoma, discuss the current treatment, and some of the problems attached to that, and then end by a wish list for how I'd like to see the treatment proceed.

Unfortunately, glaucoma remains a leading cause of irreversible blindness worldwide. The global prevalence has not changed during the course of my career. This is a disease predominantly in the elderly affecting a higher incidence in African Americans. It remains a chronic asymptomatic disease with no cure, requires long-term therapy and follow-up with poor compliance to both.

Interestingly, most glaucoma patients don't go fully blind, but they become visually disabled. Visual loss from glaucoma decreases the quality of life, affecting daily activities, walking, taking medications, doing housework, and preparing meals. Interestingly, driving is a big problem, 1.6 percent times greater incidence of motor vehicle accidents in the glaucoma population

compared to normal. These patients develop a fear of blindness, social withdrawal, and depression. This is a real disease with real complications.

The diagnosis of glaucoma has evolved nicely over the past 20 years. We now have very sophisticated ways of imaging the optic nerve, of testing visual fields, but the intraocular pressure remains the key component of the diagnosis and the treatment.

For years it was thought it was only patients with elevated pressure that developed this disease, but we've shown over the years, particularly in a study done here at Baltimore, at the Baltimore Eye Survey in 1991, that almost 80 percent of the patients had symptoms of glaucoma with pressures of 24 or less. So it's not just the patients with elevated pressure who get this disease.

There is some uniformity in why this occurs. We do know that elevated pressure is a result of structural changes in the trabecular meshwork and the outflow system that increase resistance to

outflow, and we also know that reducing elevated pressure is the only effective therapy for treating this disease.

Now, looking more closely at what actually happens in the meshwork and in the outflow system, this healthy trabecular meshwork over time, due to cellular stresses, aging, oxidation, develops fibrosis, stiffness and contraction of the tissue, reducing aqueous perfusion through that tissue, elevating pressure, and then causing optic nerve damage and visual loss. Unfortunately, the commonly used medications that we use today do not target the diseased trabecular meshwork.

How do we treat this disease? Well, this is a list of the six categories we have in glaucoma, and the modern era actually started in about 1978 when timolol was FDA approved and launched in this country. It has become and remained the gold standard upon which all new glaucoma medications are compared to, and that is in fact what netarsudil was compared to. Unfortunately, progress has been relatively slow. We haven't seen

a new mechanism of action in over 21 years.

As we look at those six categories of medications, we realize that they can fall into two types. There are medications that enhance the outflow of fluid out of the eye, and there are medications that reduce aqueous production. When one or both of those mechanisms fail, we go to surgery.

A couple of caveats here; most clinicians would prefer to enhance the outflow of fluid out of the eye, realizing that aqueous production is an important ingredient to maintain the health of the inner eye. A second caveat is that over 50 percent of glaucoma patients require more than one medication to control their pressure.

As we look at the type of medications, the categories of medications that were prescribed in 2016, the prostaglandins are the most predominant class. In fact, that's the drug that most of us will prescribe first. However, there's a large other grouping of medications that will be used.

Some patients are intolerant to medications,

but the fact is that a single medication only controls pressure in about 50 percent of patients, and the rest of those, these medications are used as an adjunct to better control the pressure, and these non-prostaglandin drug classes are required to adequately treat glaucoma.

Unfortunately, compliance is difficult. You get to more than one medication and you have more than one application, and the dosing varies from once a day up to 4 times a day. This places a major burden on the patient's daily activities and makes compliance for the patient quite challenging.

As we look at the side effects of these medications, it's impressive not just from the standpoint of ocular side effects but systemic side effects. All of them have some degree of systemic side effects, some more than others. On the ocular side effects, all of them have hyperemia as a side effect, but what is a greater concern is the systemic side effects, particularly with the beta blockers, and we'll go into more detail in a minute.

Let's talk about side effects from the standpoint of the most commonly used medications. The prostaglandins are often the first line of attack against glaucoma, and as we see here, some of the ocular side effects are pronounced, and patients are quite concerned.

Iris darkening from latanoprost and the other prostaglandins is a well-known entity in about 8 to 10 percent of patients. Peribulbar skin changes, particularly a problem in African Americans, darkening of the skin around the eyelids.

Another problem is enophthalmos, loss of orbital fat with long-term use of these prostaglandins. These are all recognized side effects, some of which are not reversible, particularly the iris darkening.

When the prostaglandins aren't used, the beta blockers are probably the second most commonly used medication, and many physicians are unaware of the systemic absorption of this drug. A dose of one drop of 0.5 percent timolol solution to each

eye has a comparable peak plasma concentration of a 10-milligram oral dose, and many of these patients are taking this twice a day, particularly in the combination products.

These physicians are unaware that this drug, this eye drop that seems to be so benign, particularly to the eye because it has so few ocular side effects, can cause bradycardia, AV block, systemic hypotension, symptoms of heart failure, drowsiness, depression, and loss of libido, very serious side effects from just a single eye drop.

The third and fourth most common categories are the alpha agonists, the CAIs. These are well known to cause follicular conjunctivitis, redness, and blepharitis, so all serious ocular problems and systemic problems attached to current medications. And this leads to the limitations of current medical therapy in that none of them treat the diseased trabecular outflow system.

They all have systemic side effects. The first line therapy does not optimize IOP reduction.

What I'm saying here is we'd like to see an eye drop that controls pressure 24 hours a day that doesn't have tachyphylaxis, and has better control of pressure.

Fourth, the adjunctive medications all increase the complexity of dosing requiring 2-, 3-, or 4-times a day applications. It is interesting that there's been multiple efforts to try to find a combination prostaglandin/beta blocker, none of which have been able to pass through an FDA approval process because they didn't add enough IOP efficacy, so it's been a challenge for us to treat these patients given these limitations.

Now one could argue we have new surgical options out there. Well, glaucoma surgery is not as ideal as it might seem. Laser trabeculoplasty, a very safe procedure, has a success rate of about 50 percent at two years. It fails. It can be repeated, but there is potential damage to the meshwork.

Incisional surgery, trabeculectomy, has well recognized complications, and these are quite

serious ones. And it also fails at about five years with only 50 percent of patients maintaining good pressure control without additional medication.

In summary, if I was asked to seek a glaucoma medication wish list, what I would like to see would be targeted therapy for the disease trabecular outflow system. I'd like to see the outflow system develop better flow to restore -- the conventional outflow pathways to get better flow out of the eye. And because of this new mechanism, I'd like to see a drug that I could use as an adjunct to existing drugs. So if we use a prostaglandin, I'd like to be able to use a second drug that we know would be additive.

I'd like to see more effective IOP lowering. I'd like to see long-term stable efficacy. Those issues I raised earlier where we want pressure controlled 24 hours a day, particularly at night, which many of the current topical medications don't do, I'd like to see. I'd like to see the avoidance of tachyphylaxis and better IOP control.

Safety is critical. We'd like to see drugs with no drug-related systemic side effects, and with those ocular side effects that are sometimes unavoidable, we want those to be tolerable and reversible. And lastly, we want a drug that's convenient that could be used once a day to enhance compliance and quality of life.

With that, I'd like to turn this over to the chief scientific officer for Aerie and the founder, Dr. Casey Kopczynski.

Applicant Presentation - Casey Kopczynski

DR. KOPCZYNSKI: Thank you, Rick.

Good morning. I'm going to describe both our program design for the phase 3 study as well as our efficacy results. Within the program design section, I'm going to tell you a little bit more about the mechanism of action of this drug because it is relevant to how we designed our phase 3 studies. Then I will present our efficacy results and show you that netarsudil when dosed once daily has shown itself to be noninferior to timolol dosed twice daily in three adequate and well-controlled

phase 3 studies.

Studying the mechanism of action, netarsudil is a new drug class. It's an inhibitor of Rho-kinase. Rho-kinase is a serine-threonine kinase. It's known to cause contraction and act as sort of the matrix deposition in the trabecular outflow pathway.

We've shown that netarsudil lowers IOP by three mechanisms, but the primary mechanism is relaxation of the trabecular meshwork to improve trabecular outflow. We've seen that not only in our preclinical models but also in human tissue, as well as in healthy volunteers.

This slide shows on the left-hand slide histologically what happens when netarsudil is perfused into a human donor eye. The top panel is a control eye perfused with saline. The bottom panel has been perfused with netarsudil. You can see that the trabecular tissue expands, opens up additional spaces for fluid to flow through, and that reduces resistance to outflow, increasing outflow facility.

Again, we've tested the drug in healthy volunteers in humans and have confirmed that when dosed once daily for 7 days, we see an increase in outflow facility of about 20 percent.

Does the mechanism of IOP lowering matter with respect to its clinical relevance? It does for a couple different reasons. One is that, as you heard, physicians often require more than one medication to achieve the IOP reductions that are required for their patients. To do that, physicians look to the label to find medications with different mechanisms of IOP lowering.

We've shown that when we combine netarsudil with latanoprost, a prostaglandin, that those two mechanisms are complementary, and we get additional IOP lowering when using netarsudil with latanoprost.

Mechanism is also important with respect to controlling IOP throughout 24 hours. Again, as Rick mentioned, it's understood that some drug classes such as the beta blockers and alpha agonists have no ability to lower IOP through the

nighttime hours. Prostaglandins and CAIs do offer some IOP-lowering protection but are less effective at night than they are during the day at lowering IOP.

We have seen in a supportive study that we've included in our NDA that netarsudil appears to be equally effective at night as it is during the day. So we do believe mechanism matters, and it matters in terms of the clinical efficacy of the drug.

I'd like to turn now to another way in which our drug differs from some of the drugs that are currently being used, and that is the impact of baseline IOP on the IOP-lowering effect of the drug.

This is a summary of the Baltimore Eye Survey that Dr. Lewis was referring to, just shown as a pie chart. As a reminder, in that survey, it was found that the large majority of patients had pressures below 25 millimeters of mercury at the time of diagnosis.

However, if you look to see which patients

are typically enrolled in glaucoma registration studies -- and I just give two examples here -- they tend to be patients with the highest pressures. In these two examples, patients were only allowed into the study if they had pressures of at least 24 millimeters of mercury and up to 36 millimeters of mercury, representing about 20 percent of the open-angle glaucoma population.

There's a reason for focusing on the higher baseline patients in these studies, and that is that the current medications achieve larger IOP reductions at higher baseline IOPs. So it's easier to measure the IOP reductions of these drugs in higher baseline patients.

This has been shown in a number of different ways. This is just an example of one paper that provided historical data from three different latanoprost registration studies that compared latanoprost to timolol. For both drugs, as the baseline IOP increased, from left to the right on the X-axis here, you can see that the IOP reductions became larger. In fact, with every

millimeter in increase in baseline IOP, each of these drugs gained about a half a millimeter in IOP-lowering efficacy.

We found netarsudil is different. It is less affected by baseline IOP in terms of the magnitude of IOP reduction that it achieves. We saw this first in our phase 2b study, which is summarized here. In this study, we enrolled the typical population of higher pressures of 24 to 36 millimeters of mercury. The top right graph shows the IOP reductions that were achieved with latanoprost, the comparator in this study, and once daily netarsudil in blue.

We also looked at a lower baseline subgroup, as shown in the bottom right-hand corner, and we found that while latanoprost lost almost a millimeter of mercury in IOP lowering, netarsudil achieved the same IOP reduction at the lower baseline pressures as it did at the higher pressures.

The results we got with latanoprost fit with the historical data, but the data we got for

netarsudil made it clear that our drug is different with respect to the influence of baseline IOP.

To summarize then, mechanism of action does matter for a number of different reasons. One of the ways we found it matters for this drug is that it's different from the currently used drugs. It produces a similar level of IOP lowering regardless of baseline IOP, whereas current drugs tend to be most effective at high IOPs but lose efficacy as the baseline IOPs come down.

We've taken this information into our design of our phase 3 studies, and coming back now to the pie chart of the glaucoma population as defined in the Baltimore Eye Survey, we're coming down a bit in terms of the baseline IOPs in the patients that we are enrolling in our studies.

In the CS301 and CS302 studies, we're studying baseline IOPs from greater than 20 to less than 27 millimeters of mercury, representing about 30 percent of the glaucoma population. In the CS304 study, we're evaluating patients with pressures greater than 20 and less than

30 millimeters of mercury, representing about 35 percent of the population.

The design of each study summarized on this slide, in CS301, this is a 90-day safety and efficacy study comparing once daily netarsudil to twice-daily timolol. CS302 is a 12-month safety study with a 3-month primary efficacy endpoint, again, comparing once daily netarsudil to twice-daily timolol.

In this study, we also included a twice-daily dosing arm of netarsudil at the FDA's request to provide information to physicians on whether twice-daily dosing would be acceptable. In CS304, 6-month safety study but again with a 3-month primary efficacy endpoint, here again comparing once daily netarsudil to twice-daily timolol.

Each of the studies is powered to show noninferiority to twice-daily timolol, and we chose timolol as that has been the gold standard comparator for approval of all new classes of medication for glaucoma for the past 30 years.

Our noninferiority analysis is based on mean IOP at each of 9 different time points measured over 3 months. Our primary population is the per-protocol population, but we do also analyze the ITT population in our sensitivity analyses.

The different between netarsudil and timolol is evaluated using a two-sided 95 percent confidence interval, and our definition of noninferiority is that the upper limit of that two-sided 95 percent confidence interval has to be within 1.5 millimeters at each of those 9 time points over 3 months, and it has to be within 1 millimeter of mercury at the majority of those time points, so a fairly stringent definition of noninferiority.

Our inclusion and exclusion criteria were very standard for glaucoma studies, primarily enrolling adult patients with either open-angle glaucoma or ocular hypertension.

In summary, our phase 3 studies are noninferiority studies compared to timolol but evaluating what is a more common range of baseline

IOPs in glaucoma. We think this represents an advantage as it enables us to enroll patients that have typically been excluded from prior registration studies.

Now I'd like to turn to the phase 3 efficacy results. Again, there are three phase 3 studies in which we measured efficacy, CS301, 302, and 304. The results, again, were that in all three studies, we demonstrated noninferiority to timolol at baseline pressures of less than 25 millimeters of mercury. We demonstrated noninferiority to timolol in one of the studies at baseline pressures up to less than 30 millimeters of mercury, and efficacy was stable over 12 months.

I'll go into the data now. In terms of demographics, again, very typical for a glaucoma population, slightly more females than males; mean age about 65 years of age, predominantly white with about 25 percent African American population. Open-angle glaucoma patients were about two-thirds of the population; studied ocular hypertension, about one-third. And about two-thirds of patients

came in on prior therapy, and one-third were treatment naive.

Disposition at month 3 in the timolol arms, 94 percent of patients completed 3 months of dosing. For netarsudil dosed once daily, 82 to 85 percent of patients completed 3 months of dosing. For twice-daily dosing of netarsudil, 60 percent completed 3 months of dosing.

Twice-daily dosing of netarsudil was not as well tolerated as once-daily dosing, so I'll just remind the committee that we are seeking approval for once-daily dosing of netarsudil, and I'll be focusing primarily on those efficacy data.

Summary of the efficacy results for each of the individual studies is presented here. As I mentioned, we showed noninferiority of less than 25 in all 3 studies. In the CS301 study, that was a post hoc analysis. The primary analysis was in the full population enrolled, which included baseline pressures up to less than 27 millimeters of mercury. In that patient population, we met 6 of the 9 time points, and therefore, did not meet the

definition of noninferiority, which requires all 9 time points to be met.

In CS302, the primary population was those patients with baseline pressures less than 25 millimeters of mercury. In the primary analysis, we met noninferiority both in CS302 and in CS304 where the population with baselines less than 25 was also the primary efficacy population.

As you can see in CS302, we only met 7 of 9 time points, and therefore did not share noninferiority at baselines less than 27, but in CS304, we met noninferiority all the way up to baseline pressures less than 30.

Now, the conclusion of noninferiority to timolol in the primary analyses here and in the post hoc analysis in CS301 was tested through multiple different types of analyses of robustness in both the per-protocol and ITT populations, and the data were shown to be robust.

Graphically, the efficacy results are presented here. The top graph is the CS301 study showing baseline IOP on the left-hand side of the

graph, and then IOP reductions obtained at week 2, week 6, and month 3. Moving to the right, netarsudil is in blue, timolol is in gold. And you can see that netarsudil IOP lowering compared very favorably to timolol.

Similarly, in the CS302 study, where this was the primary efficacy analysis, once-daily dosing of netarsudil produced very similar IOP reductions to twice-daily dosing of timolol. Twice-daily dosing of netarsudil, shown in the dark blue line, was slightly more effective than once-daily dosing, but again, it was less well tolerated.

CS304 results shown here, and again, the results are very similar to CS301 and CS302 with netarsudil showing noninferiority at all time points.

I've included tables of the individual time points. I won't go through this in any detail in the interest of time. I'll just point out that in terms of the mean difference from timolol, the differences were very small. In this study, the

CS301 study, from negative 0.92 in favor of netarsudil to plus 0.31 in favor of timolol.

In the CS302 study, negative 0.21 in favor of netarsudil to plus 0.77 in favor of timolol, and the CS304 study, negative 0.6 millimeters of mercury to 0.56 millimeters of mercury in favor of timolol.

The CS302 study was a 12-month safety study, and in the safety portion of that study, we measured IOP at 8:00 a.m. at month 6, 9, and 12. In this graph, we've added those 8:00 a.m. time points, and you can see with the blue markers that the efficacy is maintained throughout the full 12 months of this study.

Now I'd like to address what we saw at higher baseline IOPs. Here, we tend to look primarily at the pooled efficacy analysis from all three studies. The patients with pressures above 25 represented only about one-third of the patients who were enrolled in each of these studies, so pooling that data allows for a more robust analysis.

Again, this is just a reminder of how the individual studies met or did not meet noninferiority to timolol. When we pooled the data from all three studies, we meet the criteria for noninferiority from baseline pressures of less than 30 through the lowest baselines we could measure, less than 22 millimeters of mercury.

In this slide, I present a scatter plot of the distribution of IOP reductions comparing netarsudil versus timolol. You can see each of these dots represents an individual patient and the IOP reduction that they achieved on day 90. This is again the pooled population, including pressures all the way up to less than 30.

You see that the distribution of IOP reductions is quite similar between the two drugs with the median IOP reduction being 4.2 millimeters for netarsudil, negative 4.7 millimeters for timolol, the mean reductions being minus 3.9 compared to minus 4.7 for timolol. But both drugs achieving similar maximal IOP reductions up to 12 millimeters of mercury.

If we use the same scatter plot analysis looking at individual patient responses, but this time separating the patients who came in with pressures less than 25 from those who came in with pressures above 25, you can see that for netarsudil, the distribution of IOP reductions is very similar between the lower baseline patients and the upper baseline patients. This is consistent with what we saw in our phase 2b study.

For timolol, the outcome is different. At the higher baseline patients, you see on average a larger IOP reduction. Again, this is consistent with what has been reported historically for timolol. So while timolol is, on average, in this higher baseline population more effective than netarsudil, netarsudil is still effective at achieving clinically significant IOP reductions.

To summarize, in three different phase 3 studies, we've shown that netarsudil is effective at lowering IOP. It's met noninferiority to timolol at baseline pressures less than 25 millimeters of mercury in all three studies,

baseline pressures less than 30 millimeters of mercury in the CS304 study.

I'll just point out that amongst the non-prostaglandin class of IOP-lowering drugs, netarsudil is the first to show noninferiority to timolol.

Efficacy is stable over 12 months, and in our supportive studies, we've shown IOP lowering up to baseline pressures of less than 36, equal IOP lowering during the nighttime hours as well as during the day, and that netarsudil can be combined with prostaglandins to provide additional IOP lowering in patients with glaucoma.

Now I'll turn it over to Dr. Heah to present the safety data.

Applicant Presentation - Theresa Heah

DR. HEAH: Thank you, Casey.

Good morning, everyone. My name is Theresa Heah. I'm the vice president of clinical research and medical affairs at Aerie Pharmaceuticals.

Today I'd like to provide a safety overview of netarsudil 0.02 percent. Over a thousand

clinical patients have been evaluated in 10 phase 3 and up from phase 1 to phase 3 studies. The timeline here shows, for our clinical development program, a light focus on the blue bars, which are the phase 3 studies CS301, CS302, CS304, CS303 and in addition, an observational study, OBS01.

In my presentation, I will be speaking about the safety profile in terms of systemic where netarsudil has demonstrated minimal treatment-related systemic events and the ocular safety profile of netarsudil where the ocular safety events were generally mild and well tolerated.

Total exposure in four phase 3 studies, a total of 1,128 subjects have received netarsudil 0.02 percent. The table here lists all the subjects who were exposed. I'd like to point you in the direction to the highlighted area.

The long-term safety data were evaluated in a 12-month study, which is CS302 and CS303, so a total of 574 subjects received netarsudil 0.02 percent. A very comprehensive safety evaluation has been conducted in each individual study, and in

addition, we pooled and integrated all-safety analyses from all studies. This shows a list of safety parameters fairly standard in all ophthalmology safety trials, and we evaluated this from systemic events and from ocular safety events as well.

Let's look at the overall summary of the treatment-emergent events. These events were reported as TEAEs, or treatment-emergent adverse events, for any change in the subject's ocular and/or systemic health. Any change in safety parameters such as visual acuity, visual field, ophthalmoscopy were reported as TEAEs based upon assessment by investigators.

The table here in this slide is a detailed table that shows the number of subjects who have at least one or more treatment-emergent adverse events. The second column points to netarsudil acuity and netarsudil BID, and the last column timolol BID. We have 83.3 percent of subjects with at least one or more TEAE, 20.3 percent in netarsudil BID, and 60.3 percent in timolol BID.

The majority of these TEAEs in netarsudil QD and timolol BID are graded as mild. Number of subjects with at least one or more serious adverse events was approximately 3 percent across all treatment groups.

Let's focus now on the systemic safety profile. Adverse events that were reported as non-ocular TEAE for any change in the subject's systemic health, the table here shows the number of subjects with at least one or more systemic adverse events, approximately 26 percent across all treatment groups from netarsudil QD, netarsudil BID, and timolol.

I would like to just point out to the panel here today that in our study protocol, we exclude subjects who have any contraindications or hypersensitivity to beta blockers.

In terms of the most frequently reported systemic AE, 2 percent or more of subjects are listed in this table. It shows upper respiratory tract infection, similar between all groups; headaches; and dermatitis allergy. These are the

most frequently reported systemic AEs.

In terms of treatment-related systemic adverse events, SAEs in particular, one subject was reported in netarsudil QD, and the SAE event was exacerbation of coronary artery disease. This subject is a 69-year-old Caucasian female with a long history of type 2 diabetes mellitus along with other cardiovascular diseases. This subject as well has a long history and longstanding concomitant medication such as metformin and statins and other cardiovascular medications.

This was reported by the investigator as possibly treatment related, however, our sponsor medical monitor assessed this event as non-treatment related due to the long history of cardiovascular and type 2 diabetes mellitus.

SAEs leading to death, there were three being reported in the netarsudil QD group, 2 subjects, the cause of death due to myocardial infarction; one subject, the cause of death due to cardiac arrest. All subjects had relevant medical history of cardiovascular diseases and longstanding

concomitant medications.

The study investigator has deemed these three cases as not treatment related. This was also confirmed by the patients' primary physicians and cardiologists. So the SAEs leading to death shown here were non-treatment related.

In our phase 3 studies as well, we collected relevant clinical laboratory testing, so chemistry, hematology, CBC. We also collected mean blood pressure and mean heart rate. There was no clinically relevant differences for the clinical labs and mean blood pressure except for the mean heart rate.

What we saw in the mean heart rate in the netarsudil group did not demonstrate significant reductions in mean heart rate. However, timolol reduced mean heart rate by approximately 2 to 3 beats per minute, and despite all measures as mentioned earlier, the contraindications, we excluded all patients who had any possible negative sensitivity or contraindication to beta blockers.

Just to summarize on the netarsudil systemic

safety profile, what I've shown you so far, minimal treatment-related systemic events, and the three SAEs leading to death were non-treatment related.

Let's now focus on the ocular safety profile. The number of subjects with at least one or more ocular TEAE: 79.3 percent in the netarsudil QD, 89.3 percent netarsudil BID, and 49.3 percent timolol; discontinuation of study drug due to TEAEs, 22.1 percent in netarsudil QD, 57.8 percent in netarsudil BID, and 4.1 percent in timolol BID.

Due to the higher discontinuation rate and the adverse events, hence, is the reason why we're seeking the regulatory and committee approval for netarsudil QD. For the rest of my presentation, I'll be focusing on netarsudil QD. Netarsudil BID information is provided in the briefing packages.

Treatment-related ocular serious adverse events, we have one being reported in netarsudil BID. The event was iridocyclitis in the left eye of the patient despite the patient being treated with netarsudil twice a day in both eyes. This was

deemed as related by the study investigator., however, deemed as not related by the study medical monitor.

In our original NDA in February of 2017, we submitted two completed phase 3 studies, CS301 and CS302. Here the table shows 5 percent or more pooled safety analysis of these two studies. It's a very detailed table, so I would like to point you in the direction of the three most common ocular adverse events for netarsudil, which is conjunctival hyperemia at 57.3 percent, cornea verticillata at 16.7 percent, conjunctival hemorrhage at 17.8 percent.

In this table here, I would like to show you a very comprehensive evaluation in four phase 3 studies. In our day 120 safety update in June of this year, we had two additional phase 3 studies completed, which is CS304 and CS303.

What I'd like to show here is a table of ocular adverse events at 5 percent or more. Again, the three most common ocular adverse events I showed earlier are very consistent, very similar in

the rates or the incidence.

Looking at those most common ocular adverse events that I reported earlier, looking at those that discontinued, conjunctival hyperemia was 6 percent, cornea verticillata, 3.7 percent, and conjunctival hemorrhage, 1 percent. And I'd just like to point out to the panel here today that the discontinuation due to ocular adverse events, the investigator could report one or more reasons for discontinuation, so if you look at the numbers, it may not add up.

Conjunctival hyperemia, incidence was 54.4 percent. We looked at the mean hyperemia score at 8:00 a.m. of study visit. Figure shows the line graph from baseline at each study visit up to month 12. The blue line is netarsudil QD. The orange line is timolol.

We grade this from zero to 3, so from none, mild, moderate, severe. As you can see, both lines are below 1, so both of them are within mild. Conjunctival hyperemia, the severity did not increase with continued dosing.

We had the opportunity to look at a biomicroscopy grading, which is an objective assessment. The bar charts here show mild in blue, orange being moderate, and dark orange being severe. As you can see here, again, the grading was zero to 3, zero being none, 1 being mild, 2 being moderate, and 3 being severe, so again from baseline all the way to month 12.

In the baseline, 20 percent of the patients do come in with mild hyperemia, and I think this is very common in clinical or ophthalmology practices. During the point of dosing study drug, the majority of them are graded as mild; approximately 10 percent were moderate, and 2 percent were severe. Netarsudil once daily hyperemia severity, using the biomicroscopy grading, did not increase over time.

What about patient awareness? Despite the higher incidence of conjunctival hyperemia, we saw that approximately 9.9 percent of subjects reported conjunctival hyperemia, and this is in the highlighted row.

We had the opportunity to ask subjects, looking at the verbatim term of the adverse event, if this was subject reported. And looking at approximately 9.9 percent, this shows that the awareness of conjunctival hyperemia by study subjects was low.

Next, conjunctival hemorrhage, this was seen in 17.2 percent in netarsudil QD group; 1 percent discontinued as the reason for conjunctival hemorrhage. The majority of these patients, 92.4 percent, were graded as mild; 6.3 percent, moderate; and 1.4 percent, severe.

The images here show the conjunctival hemorrhages. They are coded or MedDRA coded to our studies. The far left are conjunctival hemorrhages that will be graded as moderate. The far right would be graded as mild. These conjunctival hemorrhages, the vast majority of these are small. They're transient. They're self-resolving without medical intervention and also with continued dosing.

Cornea verticillata, this was first reported

in our phase 3 studies. What is cornea verticillata? It basically refers to whorled keratopathy that we are very familiar with in ophthalmology practices that are due to amiodarone. So these are whorl-like pattern of cornea deposits typically at the basal layer of corneal epithelium.

Subjects are asymptomatic. There will be no complaints of halos or glare. The onset was typically 6 weeks for the netarsudil QD. So the images here show a biomicroscopy examination. The far left, netarsudil QD, dusting of corneal deposit, this would be graded as 1, and the far right cornea verticillata would be graded as 2. This is from the netarsudil subjects.

Upon recognizing the reporting from investigators in our phase 3 trials where we seek to understand the course of cornea verticillata, there's been a variety of drugs, cationic and amphiphilic drugs that causes the verticillata; antiarrhythmic, amiodarone that's been approved since 1984, is one of the main ones that we see in clinical practices, among others that are listed

here.

We conducted a very standard in vitro fluorescein-based assay to further understand cornea verticillata that was induced by netarsudil. This is based on Chinese hamster ovary cells. The images show the results of this. The far left is the control group, middle panel being amiodarone-treated group, and far right, the netarsudil-treated group.

What it shows is the focal accumulation of phospholipids in lysosomes, and the cause of netarsudil-induced cornea verticillata is due to phospholipidosis.

With the information that we had, we discussed with the FDA panel what are the other things that we need to do to further understand cornea verticillata. One of the questions was did cornea verticillata impact visual function.

Upon the advice, we proactively conducted a long-term observational study, which is OBS01. These are patients who have completed our CS301 and 302 study. We followed them up in the

observational period, or the extension period, without any further study-drug dosing. Forty-seven subjects were enrolled in the study of which 45 completed in this observational study.

In this study, what we did was we continued to collect visual acuity information. We collected contrast sensitivity information using Pelli-Robson charts. In addition, we collected visual function 14 questionnaire.

The conclusion or summary of this study shows that there are no clinically meaningful differences or changes in the visual function. All subjects have resolved in terms of cornea verticillata upon discontinuation of drug. Two subjects to date have improved to grade 1, so they stabilized since the beginning of this year. So cornea verticillata in our follow-up observational study did not impact visual function.

Just to summarize the three most common netarsudil ocular treatment-emergent adverse events, one, conjunctival hyperemia, 54.4 percent, the sporadic severity did not increase with

continued dosing. Cornea verticillata, 20.9 percent, and patients are asymptomatic and from the results of our observational study did not impact visual function. Conjunctival hemorrhage, 17.2 percent, vast majority mild in severity, transient, and self-resolving without medical intervention.

Other safety parameters, corneal endothelial cell count, these were conducted using corneal specular microscope at baseline and also at month 3. This was conducted in our CS302 study. The table below in this slide shows the parameters that we collected, which is endothelial cell density, coefficient variation, and hexagonality.

The results here were read by a centralized reading center and confirmed by them that there's no cell loss in the netarsudil-treated group. Also, the changes from baseline were small and not clinically relevant between treatment groups.

As ophthalmologists, we always look at vision as an important safety parameter. We looked into more detailed vision blurred events; 7.4

percent was reported in the netarsudil QD group. We tried to understand why the subjects were reporting these at every visit, so a very detailed table here shows the consecutive visits that they're being reported.

If you look at row number 2 or two consecutive visits, 27.4 percent of those that reported treatment-emergent vision blurred reported it at two consecutive visits. But as you can see, not all patients reported at every single visit. Vision blurred events reported by the subjects were intermittent.

What's the cause of the vision blurred? So we look at all the concurrent ocular surface adverse event reporting as well. There's a very detailed list here, again numerically very small. Vision blurred reported in the netarsudil group did not demonstrate a direct association with ocular surface adverse events.

Vision acuity reduced, 5.2 percent being reported. Again, we look at the number of consecutive visits being reported. This objective

assessment of visual acuity reduced events were transient or sporadic.

In terms of direct association with ocular surface adverse events, again, here we look at a very detailed ocular surface adverse event terms. There is no direct association with visual acuity reduced and ocular surface adverse events.

Other safety parameters were visual fields and cup-to-disc ratio. Here, there is no clinically relevant differences between groups, and we don't expect to see progression of glaucoma disease in these studies.

Ophthalmoscopy, we examined the back of the eye, and we look at all the adverse events being reported. Again here, no clinically relevant differences in the ophthalmoscopy safety assessments in netarsudil and timolol treatment groups.

Ocular comfort tests, ocular comfort was assessed at the 8:00 a.m. study visit by querying the subjects, "Did you experience any discomfort upon instillation of eye drops?" Subject responses

are recorded using a standardized scale: none, mild, moderate, severe.

As you can see, more than 90 percent of patients both in the netarsudil QD group and timolol BID group reported no ocular discomfort or mild discomfort, and the adverse events of instillation site pain with instillation site discomfort are fairly similar between netarsudil QD and timolol BID group.

Netarsudil 0.02 percent once daily, we've had exposure of more than a thousand patients now used by approximately 200 ophthalmologists and optometrists. In fact, today with our other programs, we have more than 2,000 patients; systemic profile, minimal drug-related systemic events. Ocular safety events were the majority conjunctival hyperemia, cornea verticillata, and conjunctival hemorrhages. However, these are generally mild, sporadic, and severity did not increase with continued dosing.

I'd like to summarize that netarsudil 0.02 percent once daily has demonstrated a

favorable safety profile with no serious life-threatening treatment-related systemic events. The discontinuation rate is very similar to what we see historically in the new class registrational trials. Timolol is known to have a very good ocular safety profile, however, less so in the systemic events.

You've heard earlier that Dr. Kopczynski had spoken about the effectiveness of IOP lowering with netarsudil, and with that, it will be a pleasure to bring up Dr. Janet Serle, who will discuss benefit-risk of netarsudil.

Applicant Presentation - Janet Serle

DR. SERLE: Good morning. I'm professor of ophthalmology and glaucoma fellowships director at the Icahn School of Medicine at Mount Sinai. I serve on several advisory boards, including Aerie. I received travel funds, honoraria, and research funds from several companies, including Aerie. I am an Aerie shareholder. I have been in clinical practice for over 30 years. My practice is dedicated exclusively to treating patients with

glaucoma.

The two questions I'm most commonly asked by my patients are will I go blind from glaucoma, and when will there be new treatments for my disease? I tell patients we'll work together to prevent loss of vision, but most importantly, they must show up for their visits and take their medications. I individualize care for each patient because response rates and side effects vary both initially and with chronic dosing.

Dr. Kopczynski has nicely demonstrated the efficacy of this new drug netarsudil. We have seen statistically significant and clinically significant intraocular pressure lowering at all baseline levels up to 36 millimeters of mercury.

This drug administered once daily is noninferior to timolol which was administered twice daily and is the only non-prostaglandin agonist to meet the noninferiority criteria compared to timolol; thus, similar efficacy to timolol without the known systemic side effects. Intraocular pressure reductions were stable, which we need for

chronic dosing.

This scatter plot, which you saw earlier, I found very powerful. It reminds us patients are not means, medians, or averages. They're individuals with great, wide variations in pressure responses. None of the current treatments, medications, lasers, or the aggressive surgical procedures we perform reduce intraocular pressure in all patients.

What this scatter plot shows us is very significant pressure reductions in the majority of patients treated with netarsudil up to 12 millimeters of mercury. I as a clinician would like to have this as an option for treatment for all of my patients.

This is a new drug class, which is very exciting. It acts differently than the ones we currently use. It enhances trabecular outflow. I anticipate it will be additive to the other classes, three of which reduce IOP primarily by decreasing aqueous humor formation.

Additivity to prostaglandins, as mentioned

previously, has been shown in this fixed-dose combination study. You see the fixed-dose product in green, which is more efficacious than either lantanoprost alone or netarsudil alone.

Our patients have difficulty complying with frequent dosing, particularly the elderly. They're forgetful. They often have caregivers, professional or family members, that are only available for limited hours during the day. So this drug, which is administered once in the evening, similarly to lantanoprost or the other prostaglandins, could be administered, and then five minutes later, the prostaglandin could be administered. Thus, all the dosing could be done once in the day.

Beta blockers, which are commonly used, when prescribed once daily are given in the morning, and this split dosing throughout the day leads to reduced compliance.

I envision netarsudil as a single-agent therapy as the efficacy is similar to timolol and the dosing is once daily. It will be an excellent

adjunct agent as, again, the dosing is once daily, less frequently than selective alpha adrenergic agonists or topical CAIs, which must be dosed 2 to 3 times daily.

You've heard from Dr. Heah about the side effects, and overall, it appears that the side effect profile is tolerable. There are few, if any, systemic-related side effects, treatment-related systemic side effects. Ocular side effects are mostly mild, sporadic, and reversible.

There were three side effects that were most commonly encountered. Hyperemia, we see with all of the drugs available to treat glaucoma. We've accepted this, both patients and physicians, as a tolerable side effect.

Conjunctival hemorrhages were small, primarily visualized on slit-lamp magnification, but they do not appear to be associated with or cause any ocular pathology. Cornea verticillata were observed, and as you saw from the observation study, were not associated with changes in visual function.

We as ophthalmologists are very familiar with corneal verticillata as they occur in over 98 percent of patients on the systemic drug amiodarone. This drug was approved in 1984. Thus, we've seen these findings for decades. We know verticillata in this patient population rarely interferes with vision and are typically reversible within 3 to 20 months after stopping treatment.

When I go to add a new medication for my patients, I discuss the side effects of each medication. You can see a patient of mine in the photo here who we treated in one eye with prostaglandin, and you can see the typical side effects and the marked asymmetry, the darkening of the iris, lengthening of lashes, and pink discoloration of the lids.

When I think about a beta blocker, I often will consult with the patient's primary care physician as this class of compounds is associated with many systemic side effects, several of which listed here can reduce quality of life. Additionally, they should not be used in patients

with pulmonary disease.

With alpha adrenergic agonists, we discuss with our patients dry mouth, headache, and fatigue, and topical carbonic anhydrase inhibitors, we know cause variability in taste, stinging, and blurred vision.

If I have and when I have the opportunity to discuss netarsudil with my patients, I will let them know it is an effective medication to reduce intraocular pressure. It's administered once daily in the evening, associated with minimal, if any, systemic side effects. Your eyes may get red, but you're used to that from your other eye drops. I may observe on slit-lamp magnification cornea verticillata and/or small hemorrhages. Neither of these affect your vision nor the health of the eye.

How will I and my colleagues use this new drug when available? Certainly, as a monotherapy, single agent, particularly in patients who would prefer to avoid the side effects you've seen with the prostaglandins. And there are patients who can't tolerate prostaglandins or are not well

responsive in terms of IOP effect to prostaglandins.

There are many patients in whom we cannot prescribe beta blockers and many patients in whom the 2 to 3 times daily dosing of alpha adrenergic agonists and topical carbonic anhydrase inhibitors is not realistic for their daily schedule.

We've seen that netarsudil is additive to prostaglandin, so it will be an excellent adjunct agent. Again, the difference in mechanism suggests it will be an excellent addition to our other agents that we use to treatment glaucoma. The once-daily dosing is a great benefit for our patients.

As Dr. Lewis described, after glaucoma surgery, 50 percent of our patients are back on eye drops. It will be nice to have this as an option.

Many of my patients and my colleagues' patients are elderly. They're in their mid to late 80s and 90s. They're losing vision from glaucoma because we don't have treatments to adequately control their eye pressures. They often prefer not

to, we prefer not to, and their primary care physician prefers not to perform surgery. They may have other medical comorbidities.

They may be on anticoagulants, and it may be very difficult for them to come to the office for the multiple post-op visits that are required. This drug may allow these patients to maintain their vision throughout their lifetime and avoid surgery.

When the patients ask when will I have a new medication, I tell them netarsudil under investigation is an exciting new drug for lowering IOP. We've heard about the benefits of this drug. We've seen that it is efficacious, both clinically and statistically. We weight the risk of vision loss and blindness with the tolerable ocular side effects we've seen today.

Netarsudil is an effective, convenient, safe, and important new medication that will help physicians meet the needs of their patients. Thank you. I'm going to turn it over to Marv.

MR. GARRETT: We have presented the safety

and efficacy data today on our new drug netarsudil ophthalmic solution 0.02 percent. As we have seen, the product is both safe and effective for the intended use. We respectfully look forward to any discussion, answer any questions, and to the vote. And we, like Dr. Chambers who mentioned earlier, look forward to working collaboratively with the Food and Drug Administration in bringing new therapies for this area, glaucoma, to market. Thank you.

Clarifying Questions

DR. CHODOSH: Thank you very much. We are just about five minutes behind schedule, but I think we'll make it up during the day.

This is our time -- and we may have some time again later, but the question is, are there questions for Aerie Pharmaceuticals from the members of this panel? If you have a question, please remember to state your name for the record before you speak, and if you can, please direct questions to a specific presenter.

From the panel? Dr. Hawkins?

DR. HAWKINS: Randy Hawkins, a substantial number of African American patients in my population. I was pleased to see an enrollment of that population in the study. Do we have any information about efficacy breakout for demographics groups where this drug as prescribed?

DR. KOPCZYNSKI: Yes. We have looked separately at the response in African Americans versus Caucasian patients. I can bring up a slide for that now.

E-178, slide up. This compares the non-Caucasian versus Caucasian patients. The vast majority of non-Caucasian were African American patients. You can see there's similar IOP-lowering efficacy, slightly different in favor of IOP reductions in the Caucasian group, but not what we would consider to be a clinically significant difference between the two.

DR. CHODOSH: Geoff, go ahead.

DR. EMERSON: Geoff Emerson. My question is why is there boric acid in the solution, and why is the pH buffered to 5?

DR. KOPCYNZSKI: In order for the active ingredient to remain in solution, the pH needs to be on the lower end. Boric acid is used as the buffer, and it is a very weak buffer. So even though at pH 5 -- you might recall in the tolerability study relative to timolol, they were similarly well tolerated, that is a low proportion of patients reported any stinging. That's because the buffering is very weak and the tear film has natural buffering capability.

DR. CHODOSH: I had a question. James Chodosh. Can you address the use of this drug or your study results in children? If I recall correctly, but didn't hear about today, the intent was to enroll patients under 2 years old and older than 18. What about the less than 2 years old, and what about those just under 18?

DR. KOPCZYNSKI: We were not successful in enrolling patients in the zero to 2 range.

Dr. Heah, would you like to talk about that?

DR. HEAH: Theresa Heah, vice president, clinical research and medical affairs. Yes, we

enrolled 2 subjects at 14 years old and 11 years old in the trial. Slide up, please, S-349.

These are the two subjects that were enrolled in the trial. We made every effort to enroll those that were zero to 2 upon the amendment of protocol, however, we didn't enroll any patients, and also because their disease is slightly different with their earlier age. But these two patients that were enrolled, they had no ocular adverse events. The IOP lowering was good.

DR. CHODOSH: A follow-up question, if I might. Do you have any specific safety concerns to the development of life, a young person, pregnancy? Can you address those issues?

DR. HEAH: We did not collect any information. We didn't allow patients who are pregnant into the study. We ensured, as part of our inclusion-exclusion criteria of our trial, that both patients, clinical subjects, and their partners utilized acceptable contraception.

DR. CHODOSH: I understand that, but I also understand that patients in practices, some of whom

will be pregnant and some of whom will not know that. So I'm wondering how you would address that.

DR. KOPCZYNSKI: I can address that. We did conduct reproductive toxicology studies in our preclinical toxicology workup, and We established systemic levels of the drug that could potentially impact the health of the fetus.

There was a very large concentration of drugs systemically required to cause any measurable change in the status of the pregnancy in the animals that were tested, and that was both rabbits and rats. Our systemic exposure after topical ocular administration in humans was typically less than 0.1 nanograms per mL. So the safety margin there is at least 300-fold in terms of any potential toxicities.

DR. KWON: Young Kwon. Just a question about the systemic side effects. I noted that there were 3 deaths that occurred in the netarsudil group as opposed to zero deaths in the timolol group. As I recall, in your phase 2 study, there was another death that was noted, so a total of 4

deaths in the netarsudil group.

While I agree that it's a very small number and it's unlikely, and there's no mechanism that I can think of that would lead to death, do you have any concerns about these deaths that have occurred? Most of them I think are cardiac related, and has that been statistically validated that there is statistically no difference between the two groups?

DR. KOPCZYNSKI: We do not have concerns about systemic effects of the drug. Again, the levels that we measured were at least 300-fold lower than what we've seen to be the EC50 for the ability of this drug to have any impact on cell shape or actin cytoskeleton, which is how it causes changes in smooth muscle cell, for example.

So there's simply too little drug to go systemically relative to the data we have for the concentrations of drug required to cause changes in these cellular functions that the drug targets.

Regarding statistics, I'd like to ask Dr. Usner to address that.

DR. USNER: Dale Usner, paid statistical

consultant to Aerie. The results are not statistically significantly different.

DR. CHODOSH: Sidney, go ahead, please.

DR. GICHERU: Sidney Gicheru. In using prostaglandin analogues in private practice, hyperemia can be a problem early on and can sometimes affect compliance. I had two questions.

One, did we look at the incidence of conjunctival hyperemia compared to prostaglandin analogs, and two, how does the hyperemia -- does it get worse, better, or is it pretty stable with time?

DR. KOPCZYNSKI: Yes. I can answer that the hyperemia appears to be quite stable over time. You might remember a line graph that Dr. Heah showed that the mean hyperemia score was less than 1 and quite stable over 12 months.

Regarding the other part of the question, maybe Dr. Heah could come up and address that?

DR. HEAH: Theresa Heah. So in respect to other -- slide up, please. It's very well known -- and I'd also like to bring up Dr. Cindy

Mattox to talk from a clinician perspective. But it's very well known that several prostaglandins such as bimatoprost and travoprost have a rate of 15 to 45 percent or 35 to 50 percent. So our incidence is within the same range.

Dr. Mattox, please.

DR. MATTOX: Cynthia Mattox. I'm an associate professor of ophthalmology, a glaucoma specialist, Tufts University, and the current president of the American Glaucoma Society. I do receive consulting fees and travel fees from Aerie, also consulting fees from other industry.

You're absolutely right. Hyperemia is something we see all the time treating glaucoma. It's very common for us to have to interact with our patients about tolerability. Certainly, we're always looking for efficacy, lowering intraocular pressure, and it's a balance. Does the intraocular pressure lower satisfactorily in order to keep the patient on the medication, and are they accepting of the consequences of the hyperemia?

The sponsor did show us that the awareness

or the discontinuation rates were very low, even though there was hyperemia reported by the investigators. And I feel satisfied with that, that it's very similar to what we see with prostaglandins.

DR. CHODOSH: Peter has the next question.

DR. ZLOTY: Peter Zloty. Question about outflow facility. I see a chart on 28 where you said that the outflow facility is improved with the use of this medication and actually worsened with placebo. I was just wondering how was that measured and if you have any data on that.

DR. KOPCZYNSKI: Slide up, please. The outflow facility was measured using tonometry, and the study was -- I'm sorry. Could you ask your question again to make sure I answer what it is you're referring to?

DR. ZLOTY: How did you know that the outflow facility improved? Did you do tonography, tonometry? What was your method, and where is your data?

DR. KOPCZYNSKI: Yes. It was tonography,

and the outflow facility was followed over time and measured in that respect. Maybe Dr. Lewis can talk to the methodology.

DR. LEWIS: Rick Lewis, chief medical officer for Aerie. The study that was shown here was done by tonography and reproduced by Arthur Sit at the Mayo Clinic, if you look at the reference here, the number 2 reference, that he presented at the American Glaucoma Society meeting in March of this year. He looked at both outflow facility as well as episcleral venous outflow and demonstrated outflow production.

DR. CHODOSH: Geoff?

DR. EMERSON: Geoff Emerson. I'm curious on the study 304, what was the discontinuation rate for the control versus the treated group? I was noting that in the 301, 15 percent of the treated group discontinued versus 6 percent of controls, and then in 302, it was 18 percent versus 6 percent. And I'm wondering if it was similar for 304.

DR. KOPCZYNSKI: Dr. Heah?

DR. HEAH: Theresa Heah. The discontinuation of CS301 at 3 months was approximately 15 percent, and it was similar as well in CS304 at 3 months. So that was our primary efficacy analysis that occurred at month 3. So at 3 months, it was similar at 15 percent.

DR. CHODOSH: Marla, go ahead.

DR. SULTAN: Marla Sultan, industry representative. Just a question. I see that you've asked that one question to the patient about the experience in terms of comfort. I was just wondering if there are any other patient-reported outcomes or questionnaires included within any of the studies. I didn't see anything mentioned.

DR. KOPCZYNSKI: Dr. Heah?

DR. HEAH: Theresa Heah. The only test that we did, a questionnaire, was ocular comfort test.

DR. CHODOSH: I'm going to take the prerogative of asking the last question before the break, and then we probably will have time later to ask more questions because we need to move on. But my question was for Dr. Lewis, and that was, do you

think that this drug will have particular benefit to normal-tension glaucoma?

I'm not a glaucoma specialist, as most of you know, but it occurred to me that there are patients in whom we'd like to lower the pressure below normal, but we know that the existing drugs don't do that very well.

Can you comment on that, please?

DR. LEWIS: Frankly, I think you've hit upon an important part of the studies here is that the ability of netarsudil to help lower pressure in lower pressure patients is very exciting and a great opportunity because that is the big challenge. Many of our drugs will get the pressure down, perhaps down to 19 or 20 or 21 within a single or even two agents, and trying to get them much lower. A large percentage of the population, as we all know, particularly certain racial groups like the Japanese who have a low-tension glaucoma problem, this is a very exciting opportunity.

Casey presented a little brief introduction into the Mercury program, which is the combination

of lantanoprost and netarsudil, and the responder rate is very, very exciting. And I think we in glaucoma look forward to getting access to that.

DR. CHODOSH: Thank you.

We're going to take a break, which will end at 10:15. Panel members, please remember, no discussion of the meeting topic during the break amongst yourselves or with anyone else. Thank you.

(Whereupon, at 10:05 a.m., a recess was taken.)

DR. CHODOSH: Welcome back. We are now going to proceed with the presentations by the FDA.

FDA Presentation - Sonal Wadhwa

DR. WADHWA: Good morning. My name is Sonal Wadhwa. I'm a medical officer here at the FDA in the Division of Transplant and Ophthalmology Products, and I'll be giving the clinical perspective for netarsudil.

We've already gone over we're talking about netarsudil, which is a Rho-kinase inhibitor. It's a topical ophthalmic solution. The proposed dosing regimen is one drop in the affected eye once daily

in the evening, and the proposed indication is for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

My talk will be focusing on four studies. The first two, 301 and 302, as we know and have discussed, were both double mass randomized, multicenter, active controlled studies. 301 had two arms, netarsudil once a day and timolol twice a day. There were 411 subjects. This was a 3-month study, and the baseline IOP was less than 27.

Study 302 had three arms, netarsudil once a day, netarsudil twice a day, and timolol twice a day. The study had 756 patients. It was a 12-month study, and patients here also had a baseline pressure of less than 27.

Study 304 was also a double-mass, randomized, multicenter, active controlled study. There are two arms, netarsudil once a day and timolol twice a day. There are 708 patients. This was a 6-month study, and here the baseline pressure was less than 30 compared to the 27.

The fourth study I will be talking about today was the observation safety study, OBS01. This was an observational prospective study, noninterventional, and there were 45 patients, and there was no set duration.

Moving on to the subject disposition for each study, I'll start with 301. You can see that there was a discontinuation rate of approximately 15 percent in the netarsudil group compared to 6 percent in the timolol group. The majority of the subject discontinuations were secondary to AE in the netarsudil group.

In study 302 at 3 months, there was a 18 percent discontinuation rate in the QD group, 40 percent in the BID group, and 6 percent in the timolol group. This was a longer study, as mentioned, so at the 12 months, there was a 42 percent discontinuation rate in the netarsudil QD group, and 66 percent in the BID group, and 19 percent in the timolol group. Again, in the netarsudil group, the most common reason for subject discontinuation was AE.

Study 304, the discontinuation rate in the netarsudil group was 31 percent compared to 12 percent in the timolol group. Again, the most common reason for subject discontinuation in the netarsudil group was AE.

Moving on to the efficacy, in study 301, the primary efficacy outcome was the mean IOP at three time points, 8:00 a.m., 10:00 a.m., and 4:00 p.m. at three visits, which were week 2, week 6, and month 3.

The criteria for noninferiority was based on the upper limits of the 95 percent confidence interval for the treatment difference between netarsudil and timolol. It had to be within 1.5 millimeters of mercury for all 9 time points and within 1 millimeter of mercury for the majority of time points.

The study 301 did not meet the prespecified endpoint with the per-protocol or the ITT analysis. I know this is a lot of information here, so just to give a brief summary, this is study 301. This is the per-protocol population with observed data.

All patients were included. This was baseline of less than 27, and the areas highlighted in red show where the criteria for noninferiority was not met.

This is the same study 301. Now we're looking at a different population. This is the ITT with LOCF. Again, the areas in red show where the criteria for noninferiority was not met.

Although 301 did not meet the prespecified endpoint with the per-protocol or the ITT analysis, when looking at a post hoc analysis of patients with pressures less than 25, it did meet its endpoint in both the per-protocol and ITT populations.

This is still study 301. Here we're looking at the per-protocol population with observed data. As I mentioned, this is a post hoc analysis, and here we'll be looking at patients with baseline pressures of less than 25 compared to the previous slides where the pressures were less than 27. Looking at these results, the criteria for noninferiority was met.

Moving on to study 302, the primary efficacy

outcome was the mean IOP for subjects, and here it was prespecified for baseline pressures less than 25 at the same three time points, 8:00 a.m., 10:00 a.m., and 4:00 p.m., at the same three visits, week 2, week 6, and month 3. Study 302 did meet the prespecified endpoint with both the per-protocol and ITT analysis.

This is now study 302. This is the per-protocol population with observed data. As I mentioned, they prespecified only looking at patients with a baseline pressure of less than 25, and here the criteria for noninferiority was met.

Looking at the same study, 302, this is now the ITT with LOCF population. Again, we're only looking at patients with baseline pressures of less than 25. The criteria of noninferiority was met.

Now, I will hand it over to my statistical colleague to continue their talk with their statistical perspective and continue the discussion with the results of study 304.

FDA Presentation - Yunfan Deng

DR. DENG: Good morning. My name is Yunfan

Deng. I am the statistical reviewer for the application of netarsudil. I will present the agency's statistical evaluation of efficacy.

Our efficacy evaluation focused on the three phase 3 studies, studies 301, 302, and 304. The three studies were similarly in their design. They were multicenter, double-mass, active-controlled, noninferiority studies. The main differences among the studies are noted in the table.

Studies 301 and 304 both had two treatment arms, netarsudil once daily, QD, and the active comparator, timolol twice daily, BID. Study 302 had an additional netarsudil twice-daily arm. The applicant is seeking approval for only netarsudil QD, therefore, I will focus on the netarsudil QD efficacy results.

The treatment duration was 3 months in study 301, 12 months in study 302, and 6 months in study 304. Regarding baseline IOP entry criteria, studies 301 and 302 enrolled subjects with baseline IOP lower than 27, while study 304 enrolled subjects with baseline IOP lower than 30.

The protocol design primary efficacy endpoint was mean IOP in the study eye at 8:00 a.m., 10:00 a.m., and 4:00 p.m. on days 15, 43, and 90. The mean IOP change from baseline in the study eye at the 9 post-baseline time points was a secondary endpoint. There were two protocol-defined efficacy analysis populations, intend-to-treat and per-protocol populations.

The ITT population included all randomized subjects who received at least one dose of study drug. The per-protocol population was a subset of the ITT population, including subjects who had no major protocol violations likely to seriously affect the primary outcome of the study.

The protocol defined primary analysis method evaluated the treatment difference using a 95 percent confidence interval based on 2-sample t-distribution at each individual time point. In study 301, the primary analysis was conducted on the per-protocol population using observed data. In studies 302 and 304, the primary analysis was conducted on a subset of per-protocol subjects,

specifically the subjects with maximal baseline IOP less than 25. This subset was selected based on the positive post hoc results from study 301.

Additional analysis based on ITT were also conducted. The applicant also analyzed the primary endpoint using various methods of handling missing data under varying assumptions.

The protocol designed successful criteria for noninferiority were based on the upper limits of the 95 percent confidence intervals. For the treatment differences, the upper limits needed to be within 1.5 for all 9 time points and within 1.0 for at least 5 out of the 9 time points.

This table has two parts. The first part presents subject disposition, and the last three rows present the percentage of per-protocol subjects of the overall ITT population. For subject disposition, we focused on discontinuation due to adverse events since discontinuation due to other reasons were comparable between the two treatment groups.

All studies showed significantly higher

discontinuation rates due to AE in the netarsudil group compared to the timolol group. The discontinuation rates prior to month 3 due to AE ranged from 10 percent to 12 percent in the netarsudil group for the ITT population compared to 1 to 2 percent in the timolol group. Our clinical reviewer will discuss these AEs in further detail later.

The per-protocol population consisted of 82 percent to 90 percent of the ITT subjects for the three studies. We illustrate the percentage of subjects in each of the two subgroups, baseline IOP less than 25 or greater than/equal to 25.

As mentioned previously, studies 301 and 302 enrolled subjects with baseline IOP less than 27, whereas study 304 enrolled subjects with baseline IOP less than 30. The prespecified analysis population for studies 302 and 304 included only subjects with baseline IOP less than 25.

Approximately 60 to 65 percent of subjects in all studies has maximal baseline IOP less than 25. In study 304, among the subjects with baseline

IOP greater than 25, about half of them had baseline IOP between 25 and 27, and the other half had baseline IOP between 27 and 30.

A summary of the applicant's key efficacy results for the three studies is presented. For subjects with baseline IOP less than 25, that is, the first and the middle column, the noninferiority criteria were met for all analyses except for the baseline observation carried forward, BOCF analysis in study 302.

For subjects with baseline IOP less than 27, only study 304 met the noninferiority criteria for the three analyses. As mentioned previously, study 304 enrolled subjects with a broader range of baseline IOP, including baseline IOP up to 30. For these subjects, the noninferiority criteria was only met in the per-protocol observed analysis.

Based on these results, it appears that netarsudil may not work as well as timolol for subjects with higher baseline IOP.

As previously mentioned, mean IOP changed from baseline, and the post-baseline time points

were protocol defined secondary endpoints and form the basis for desired label claims. We conducted various analyses of this point to gain insight into the IOP-lowering effect of netarsudil.

The analysis of covariance ANCOVA adjusted for baseline IOP is a statistically preferable analysis method since baseline IOP may be a prognostic factor for the efficacy outcome. Therefore, the results I will present are based on the ANCOVA adjusted analysis.

Of note, the results are generally consistent with the unadjusted analysis. In addition, the results are presented by maximal baseline IOP less than 25 and greater than/equal to 25.

The per-protocol observed analysis results are presented in the next few slides since this analysis was the protocol defined primary efficacy analysis, and the results were generally consistent with those of the ITT analysis.

Mean IOP change from baseline in study eye by visit and time for study 301 is presented in

this table. The left side of the table presents the results of mean IOP change from baseline for the subgroup of subjects with baseline IOP less than 25, and the right three columns of the table present the results for subjects with baseline IOP greater than 25.

The results for the netarsudil group from day 15 to day 90 are denoted in blue, and for timolol group are denoted in red. In study 301, as you can see, within each subset, the two treatment groups have comparable mean baseline IOP. For subjects with baseline IOP less than 25, mean IOP reduction from baseline ranged from 3.6 to 5.1 in the netarsudil group and from 3.2 to 4.7 in the timolol group.

The two treatment groups had similar mean IOP reduction. As you can see from the table, the upper bounds of the 95 percent confidence interval met the noninferiority criteria.

For subjects with baseline IOP greater than 25, mean IOP reduction from baseline ranged from 2.2 to 4.9 in the netarsudil group and from 4.6 to

6.0 in the timolol group. Compared with the timolol, the netarsudil group had a smaller mean IOP reduction at all morning time points and on days 43 and 90 as denoted in the bold red color in this table. The treatment differences were most noticeable at 8:00 a.m. and 10:00 a.m. on days 43 and 90 and as high as 3.0.

This is a graphical presentation of the mean IOP change from baseline by visit and time for study 301. The left panel presents the results for subjects with baseline IOP less than 25, and the right panel for subjects with baseline IOP greater than 25. The blue line denotes the netarsudil group, and the red line denotes the timolol group. Please note that lower values on this graph correspond with higher IOP reduction.

On the left-front panel, you can see that the two treatment groups had similar mean IOP reductions, and on the right panel for subjects with baseline IOP greater than 25, the netarsudil group had much smaller mean IOP reduction at a majority of the time points. The treatment

differences were most noticeable at 8:00 a.m. and 10:00 a.m. on days 43 and 90.

In study 302 within each subset, the two treatment groups had comparable mean baseline IOP. For subjects with baseline IOP less than 25, mean IOP reduction from baseline ranged from 3.4 to 4.6 in the netarsudil group and from 3.7 to 5.1 in the timolol group.

The two treatment groups had similar mean IOP reductions. As presented in the table, the upper bounds of the 95 percent confidence interval met the noninferiority criteria. However, for subjects with baseline IOP greater than 25, mean IOP reduction from baseline ranged from 3.4 to 4.9 in the netarsudil group and from 4.3 to 5.9 in the timolol group.

Compared with timolol, the netarsudil group had a smaller mean IOP reduction at all morning time points and at days 43 and 90. The treatment differences were also most noticeable at 8:00 a.m. and 10:00 a.m. on days 43 and 90.

This again is the graphical presentation of

the mean IOP change from baseline by visit and time for study 302. Similar as study 301, on the left panel, you can see that the two treatment groups have similar IOP reductions. On the right panel for subjects with baseline IOP greater than 25, the netarsudil group had a smaller mean IOP reduction at all morning time points and at days 43 and 90. The treatment differences were again most noticeable at 8:00 a.m. and 10:00 a.m. on days 43 and 90.

In study 304, the two treatment groups again had comparable mean baseline IOP within each subset, and for subjects with baseline IOP less than 25, mean IOP reduction from baseline ranged from 3.9 to 4.7 in the netarsudil group and from 3.8 to 5.2 in the timolol group.

The two treatment groups had similar mean IOP reductions, and you can see from the table the upper bounds of the 95 percent confidence interval met the noninferiority criteria. However, for subjects with baseline IOP greater than 25, mean IOP reduction from baseline ranged from 3.9 to 5.0

in the netarsudil group and from 4.4 to 6.2 in the timolol group.

Consistent with the findings in studies 301 and 302, timolol had higher IOP reduction effect compared with netarsudil at all morning time points and at days 43 and 90. The treatment differences were also most noticeable at 8:00 a.m. and 10:00 a.m. on days 43 and 90.

Again, the graphical presentation of the mean IOP changed from baseline by visit and time for study 304, on the left panel, you can see that the two treatment groups had similar mean IOP reductions. For subjects with baseline IOP greater than 25 on the right panel, similar as observed in studies 301 and 302, the netarsudil group had a smaller mean IOP reduction at all morning time points. The treatment differences were most noticeable at 8:00 a.m. and 10:00 a.m. on days 43 and 90.

In summary, for subjects with maximal baseline IOP less than 25, overall, the test drug netarsudil and active comparator timolol appeared

to have similar mean IOP reductions on days 15, 43, and 90. But for subjects with maximum baseline IOP greater than 25 compared with timolol, netarsudil had a smaller mean IOP reduction effect. The treatment differences were most noticeable at 8:00 a.m. and 10:00 a.m. on days 43 and 90.

I will hand the podium back to Sonal, our clinical reviewer, for the safety evaluation.

FDA Presentation - Sonal Wadhwa

DR. WADHWA: Moving on to safety now, I'm going to be focusing the safety talk on the same four studies I discussed earlier, 301, 302, 304, and the observation study OBS01.

Looking at deaths, there were no deaths, as we've talked about previously, in 301. In study 302, there were 2 subjects in the netarsudil once-a-day group secondary to myocardial infarction. In study 304, there was one subject in the netarsudil once-a-day group who died secondary to cardiac arrest. None of these deaths were thought to be treatment related.

Looking at the AEs, when we looked at the

pooled safety population from study 301 and 302, conjunctival hyperemia was the most common AE, 57 percent. Some of the other common ocular AEs were conjunctival hemorrhage, corneal verticillata, and instillation site pain.

Looking at study 304, here again, conjunctival hyperemia was the most common ocular AE, 48 percent. The next most common were again, corneal verticillata, instillation site pain, and conjunctival hemorrhage.

I'm going to focus a little bit on corneal verticillata. As we all know, it's a whorl-like pattern of deposits in the epithelium of the cornea. This is secondary to intracellular phospholipid accumulation in the lysosomes. It's usually bilateral, and usually patients have no visual symptoms.

As we've discussed, amiodarone is the most common cause of verticillata. Other drugs which are known to cause corneal verticillata are chloroquine, hydroxychloroquine, indomethacin, and phenothiazines. Netarsudil is the first topical

ophthalmic known to cause corneal verticillata, and because of the finding of the corneal verticillata in these studies, there was a safety study to further investigate this finding.

Looking first at the incidence of corneal verticillata in the studies, in study 301, there were 11 patients out of the 203 in the netarsudil group that developed verticillata compared to zero in the timolol group.

In 302, there were 64 patients in the QD group that developed verticillata and 64 in the BID group that developed verticillata compared to 2 patients in the timolol group. In study 304, there were 86 patients that developed verticillata in the netarsudil group compared to zero patients in the timolol group.

This observational study OBS01 was designed to follow-up and collect additional safety data in subjects who developed verticillata in studies 301 and 302. Subjects in these clinical trials were identified by searching for the following AEs: corneal whorls, corneal haze, subepithelial corneal

deposits, vortex epitheliopathy, and corneal verticillata. Any of the above in one or both eyes were eligible to participate in this study.

This observational study had no set duration, and the expectation was that subjects who consented would participate until there was resolution or stabilization of the verticillata. Subjects participating in this study were not treated with netarsudil. They did, however, restart other IOP-lowering agents as recommended by their eyecare professional.

The following information was collected on the patients: contrast sensitivity testing, thus corrected visual acuity; the VF-14 questionnaire. Corneal verticillata were graded using Orlando's grading scale from 1984. This was a grading scale used to describe amiodarone-induced corneal verticillata. Lastly, the time to corneal verticillata resolution or stabilization was documented.

I won't go over in detail the whole grading scale, but it was a grading scale of four grades

with grade 1 being mild verticillata and grade 4 being the more severe.

Corneal verticillata were graded at visit 1 and all the monthly/bimonthly follow-up visits. Subjects were followed until corneal verticillata resolved in both eyes. Therefore, an eye considered resolved at a prior visit was reevaluated if corneal verticillata remained in the fellow eye.

All corneal verticillata cases reported in study 301 were resolved by the time this observation study was initiated, therefore, there are no subjects from 301. All the data is from patients in 302.

Looking at the baseline characteristics of verticillata, the number of patients who had corneal verticillata at the study entry was 15 in the netarsudil QD group and 4 in the BID group. In terms of the duration of investigation product to the start of verticillata, it was approximately 165 days in the netarsudil QD and approximately 110 days in the BID group.

This table is looking at the mean change from baseline in the corneal deposit grading. There's a lot of information here, but in summary, as you can see, as we go in visits, there's less eyes with verticillata, and the trend is that the grading score is getting better at each visit.

Looking at mean change from baseline in visual acuity, if we look at the change from visit 2 to the final visit, you can see that in the netarsudil QD group and the BID group, there is no significant change in visual acuity.

Looking at the time from corneal verticillata start to resolution or stabilization by treatment group, the mean time in days to resolution or stabilization was approximately 496 days in the netarsudil QD group and 517 days in the netarsudil BID group.

Looking at the time from last dose to resolution or stabilization by treatment group, the mean time from last dose in days was approximately 317 days in the netarsudil QD group and approximately 419 days in the BID group.

Looking at discontinuations, as I previously mentioned, in study 301, there are 11 patients who developed verticillata. Of those, zero discontinued treatment. In study 302, I mentioned there were 64 patients in each of the QD and BID dosing group that developed verticillata. Thirteen in the QD dosing group discontinued treatment and 24 in the BID discontinued treatment.

In study 304, there were 84 patients that developed verticillata, and out of those 86 [sic], 14 discontinued treatment. At the completion of this observation study, corneal verticillata had resolved in all subjects except three where corneal verticillata remained stabilized but unresolved.

This table shows those 3 patients. It shows what their verticillata grade was at visit 1, shows what their verticillata grade was at stabilization, and of note, two of the patients were on oral NSAIDs.

I'll leave you with this slide, which is the questions we'll be discussing later in the day, and I thank you for your attention.

Clarifying Questions

DR. CHODOSH: Thank you. At this point, we're going to ask clarifying questions for the FDA. And again, for those of you on the panel, please remember to state your name for the record before you speak. And if you can, please direct your questions to either Sonal or Yunfan.

Go ahead, Geoff.

DR. EMERSON: Geoff Emerson. This is a question for Dr. Wadhwa. Is it common in a phase 3 trial to have the prespecified endpoint exclude a portion of the patients, in this case, the pressures that are over 25?

DR. WADHWA: Different trials have had different exclusion criteria. We've had trials where there are patients at less than 36 or lower inclusion criteria. It's not unusual to have prespecified IOP levels.

DR. CHAMBERS: Wiley Chambers. We do encourage people developing products to learn from prior trials. If people see a particular finding in one trial, it is not uncommon to change things

in subsequent trials or trials that are ongoing, change analysis plans to match what has been learned from a prior trial. As long as it's done prior to unblinding of the trial, we generally consider it acceptable.

DR. KWON: Young Kwon. This is a question directed at Dr. Deng. Let me see if I can say this correctly. In the earlier presentation by Aerie Pharmaceuticals, in study 304, they noted they've met the primary efficacy endpoint for all three groups, the group with baseline IOP less than 25, group with a baseline IOP less than 27, and less than 30. There was an earlier presentation in the morning.

You have just presented a subgroup analysis where in study 304, you've noted that they have met the primary endpoint efficacy in a group baseline IOP less than 25 but not for those over 25.

Trying to understand the difference in the conclusions, would it be reasonable to assume -- and this is my assumption -- that the reason why the conclusion is slightly different for

those with baseline IOP greater than 25 is that they have included all of the patients with the baseline IOP less than 27 to 30 to come up with their primary efficacy endpoint, whereas you've isolated those greater than IOP 25 to conclude that it's the primary endpoint of noninferiority was not met?

That was a long question, but do you understand the gist of my question?

DR. DENG: Yunfan Deng. I think I got your point. Specifically for study 304, the predefined analysis population is for subjects less than 25, and also, the study is powered for that population is our take. For subjects greater than 25, the study was not powered for that portion, that subset.

So anything we observed that's consistently happening in all the three studies, we can say that subjects with higher IOP had smaller mean IOP reduction effect. That's what we observed. But in terms of statistical testing, I would hesitate to draw the conclusion of noninferiority criteria not

met for that higher IOP subset.

DR. KWON: If I understand you correctly, you're saying that for that subgroup with a greater than 25 baseline IOP, the primary endpoint of noninferiority to timolol was not met; is that correct?

DR. CHAMBERS: This is Wiley Chambers. I think the issue you're getting caught up on is whether it was prespecified within the analysis plan. There was not a prespecification in the analysis plan just to look at people over 25.

We have done it, and that's why you're seeing reported observation. But without having prespecified it and therefore accounting for the alpha, we're not saying that it's a definitive finding.

DR. CHODOSH: I think there's someone who'd like to say something from the FDA.

DR. WANG: My name is Yan Wang. I'm the statistical team leader for this application. To answer the question about our conclusion regarding the result for the subjects with baseline above 25,

even though the sponsor's analysis, they make the 95th margin for the overall population less than 25 -- less than 27, I think certainly they don't make it one of their analyses.

When we are talking about results for the subset with baseline above 25, we're not focusing on statistical inference anymore. It's based on the collective evidence of here. Our conclusion is that even though sponsor has not predefined to power the study to make an inference about the subset of subjects, our conclusion is that the test product is not doing as well as timolol for this subset of people.

DR. CHODOSH: I had a question. This is James Chodosh. I had a question that relates I think to that. The applicant told us that the pressure-lowering effect is equal across all intraocular pressures, whereas timolol has a greater effect at higher pressures.

In effect, it shouldn't surprise us, I don't think, if there is a drop-off in noninferiority, if I can put it that way, that drop-off would be more

likely as you go to the higher-starting pressures. That's my interpretation of it.

I had a different question that --

DR. WANG: Can I clarify the question, the statement you make for the sponsor. If you go to slide 26 of the statistical presentation, I want to clarify that. The test product makes the 95 margin only for the subset of people with baseline less than 25. When you look at the subset with baseline less than 27, overall, they don't make it. I just want to clarify that.

DR. CHODOSH: But it was also emphasized that it wasn't powered to do that; is that correct?

DR. WANG: Even if they powered, based on what we observed in terms of the treatment difference, they were not able to show noninferiority because the point estimation favored the timolol group.

DR. CHODOSH: I had another question for Yunfan, and that is, in looking particularly in study 301, it looked to me like there was some drop-off in effect of the drug as you got later in

time. So between the first time point and the 90-day time point, it looked like the differences or the mean drop in IOP was less as you got to 90 days. In 302, it was less obvious.

Do you have any comment about a potential loss of effect over time of the drug? I was particularly looking at slide 29 actually, if you look at the graphical representation on the right.

DR. DENG: I will hand it to Dr. Chambers. He knows the disease.

DR. CHAMBERS: I think numerically there is a slight difference, but it's not statistically significant. It's not powered to look at those differences. To date, we have never seen a product have tachyphylaxis wear off at day 90 that then followed through -- at times after day 90 that didn't show up at day 90. So we've usually viewed day 90 as being sufficient for what happens long term.

DR. CHODOSH: You're not expecting this to progress more if there is indeed a trend.

DR. CHAMBERS: We believe if there was going

to be tachyphylaxis, we would have seen it at day 90, correct.

DR. CHODOSH: David, I believe you had a question.

DR. YOO: Dave Yoo. For the corneal verticillata, were there a corresponding number of patients that were on NSAIDs who ended up having resolution of the verticillata?

DR. WADHWA: I don't know that off the top of my head. I don't know if the applicant has that information.

DR. CHODOSH: We'll, I think, have some more time to ask the applicant some questions. Do we want to involve them now; is that okay?

Would someone on the applicant's side like to address that question?

Do you want to ask it again, David, please?

DR. YOO: Dave Yoo again. Really the question is, were there people on other types of medications that can cause verticillata who had resolution of the verticillata after the study was completed?

DR. HEAH: Theresa Heah. Yes, a number of our patients, because of their age group, they are on NSAIDs for all the various reasons. Of the three subjects that Dr. Wadhwa showed earlier, two of them have actually resolved. One of them was on naproxen, and they actually had resolution of the corneal verticillata, whereas another subject that was on ibuprofen or Advil, that subject has not resolved.

DR. CHODOSH: I cut off Dr. Tonya King from asking a question in the earlier session, so she's going to get her chance now.

DR. KING: Thank you. Tonya King.

I had a number of questions. First of all, in the analysis, it doesn't mention the number of subjects that may have had both eyes being treated, and I was curious whether there were individuals in the study -- it appears it was alluded to -- that had multiple eyes in the analysis and whether the analysis was adjusted for this correlation within a person or whether the eyes were treated as independent.

DR. USNER: Dale Usner, statistician, and I will call up Dr. Heah as well in a moment. The analysis was completed on a predefined study eye within each patient. So the primary analysis actually only took one eye of each patient into account, and that predefined study eye was based off of enrollment criteria at baseline. And if Dr. Heah could address that.

DR. HEAH: Yes. As ophthalmologists, we look at both eyes because the drug is being dosed in both eyes, so we had the study fellow eye. And we followed up the patients both in terms of study eye and fellow eye and per subject level as well.

DR. CHODOSH: Peter Zloty had the next question.

DR. ZLOTY: Peter Zloty, a question concerning safety. I noticed that in the pooled phase 3 data, 22 percent of the folks had to discontinue it when they were using it once a day. And when they used it twice a day, almost 60 percent.

Now, I understand we're talking about just

once a day, but we've alluded to compliance, and patients get confused. And I'm not sure I've seen any other ophthalmic medications where if the patient used an extra drop, they would have such an adverse side effect. So can you talk to whether or not the number of 22 percent of patients having to discontinue is not especially high for an application of a new medication, and at twice a day, 60 percent had to stop using the drop?

DR. CHAMBERS: This is Wiley Chambers. It is obviously higher than the control group. That's why we put the control groups in. It is not unique, groundbreaking, whatever other term.

What happens in clinical trials is different than what happens in clinical practice. In clinical trials, we tend to be more conservative, and not knowing all of what's going on, it's not uncommon to have people drop out of trials, both to study whether the effect has gone away or the seriousness of the particular effect when you don't fully understand it.

Sometimes, you will see differences in

continuation rates at different stages of development and depending on how much we know about the particular adverse event. So we don't make as much about what the particular rate is in a clinical trial the first time something gets observed. Or sometimes, it doesn't; sometimes, it gets missed.

There are some major events that were not seen initially in clinical trials. Prostaglandin analogues, for example, grow eyelashes, not observed in the original clinical trials, yet very evident when people went back and looked at it. So sometimes we don't pick up everything in every clinical trial.

DR. CHODOSH: Jo Ellen?

MS. DeLUCA: Jo Ellen DeLuca, patient rep. How much prepping do the patients get in terms of, say, vocabulary, ease with their surroundings, before they set out on the trial, or are there different amounts where people come in in surgery that day and not much prep, and somebody else has a prep with an assistant in the office who can help

them out with vocabulary and make them feel more comfortable in their surroundings? Hospitals are scary for most people.

I think that it has a lot of relevancy to the trial when you have more patients, a variety of patients, than it is to just have a few. The prepping and getting ready things at home and making them feel comfortable before they go, is that part of the process or -- especially with eyes when you think you're going to go blind.

DR. CHODOSH: Wiley?

DR. CHAMBERS: We'll defer to the sponsor to explain what preparation was done to patients, explanation to patients in the clinical trial.

DR. HEAH: Theresa Heah. To prepare the patient in our clinical trial, our study investigators at the study site explained in detail the study protocol and collected informed consent. I think in clinical trials, the investigators tend to be more hypervigilant and so are patients because it's a new class of drug.

As Dr. Chambers had mentioned earlier, it's

not unusual for us to see this in a new class phase 3 registration trial in terms of the discontinuation rate.

Slide up, please. In the previous times of Xalatan, for example, latanoprost, which Dr. Sultan might be more familiar with Pfizer, the discontinuation rate in the phase 3 trial was 25 percent versus timolol, and for Alphagan, a 12-month study, the discontinuation rate was 46 percent.

In terms of our clinical trial, we actually also ensured that patients had the compliance dosing reminder to remind them to take the drug between 8:00 to 10:00 p.m. We have a little timer, and we also have reminder cards for them to make sure that they go back to the study visits as well.

Dr. Lewis can also speak from a clinician medical monitor perspective.

DR. LEWIS: Hi. Rick Lewis, chief medical officer and medical monitor during the trials. The initial finding of the verticillata was a surprise to us as well as the investigator, and I think as

Dr. Chambers pointed out, it caused some of the investigators to have some concern and discontinue their patients in the trial.

As we became more comfortable with it, we began to inform all the investigators through investigator meetings of what to expect, what the percentages were, and perhaps the most important thing was that there was no effect on visual function. With that, subsequent investigators felt more comfortable with this side effect.

DR. CHODOSH: Thank you.

Randy, you had a question?

DR. HAWKINS: Randy Hawkins. I may have gotten an answer. I was going to ask what time, to the applicant, was the drop administered in the evening and whether the adverse effect was reported being during the daytime or the night relative to the eye symptoms.

DR. HEAH: Theresa Heah. For the netarsudil QD once-a-day dosing is dosed at night between 8:00 and 10:00 p.m. as prespecified in our study protocol. Because we are comparing with the active

comparator timolol that's dosed twice a day, when patients come back in the morning, they get their study visit at 8:00 a.m., and then they have a vehicle instillation to make sure that they are well controlled because the comparator arm is twice a day.

For the netarsudil BID group, they are dosed also after the study visit at 8:00 a.m. between our 8:00 and 10:00 a.m. So the dosing for night is 8:00 to 10:00 at night, in the morning between 8:00 to 10:00 immediately after the study visit. Our study visit, from a diurnal perspective, will collect information at 8:00 a.m., 10:00 a.m., and 1600, which is 4:00 p.m.

DR. CHODOSH: David, I think you're next.

DR. YOO: A quick question about the conjunctival hyperemia. So if we are going to be using this in an additive fashion, do you anticipate, let's say, a prostaglandin agonist, that the hyperemia could get worse, or do you think that it will just be an effect if you used these in conjunction anyway?

DR. HEAH: Theresa Heah. Actually, we have ongoing phase 3 studies in our fixed-dose combination called netarsudil/latanoprost in our Mercury program. So we have the information actually followed up in a mild [ph] fashion and also with Mercury 1, Mercury 2. We didn't see an additive increase in hyperemia. In fact, we just saw the rates being similar. As study goes by, hyperemia rates actually improve. Maybe because investigators are getting used as well to the study and patients as well, yes.

DR. CHODOSH: I think next is Mildred.

DR. OLIVIER: Thanks. Were there any differences in the patients who were naive to medications versus those that you had washed out, or did you look at that at all?

DR. KOPCZYNSKI: Casey Kopczynski. I can say that from an efficacy perspective, we did look at the efficacy in the treatment naive versus those who came in on prior treatment. In the CS301 study at the 2-week time point, there was actually an efficacy benefit selectively for patients who came

in on a prostaglandin, but other than that, in the subsequent studies, there was essentially the same IOP response, whether patients came in on prior medication or treatment naive.

DR. CHODOSH: Thank you.

Tonya is next. Please remember, everyone, to state your full name before each question or response. Thanks.

DR. KING: Tonya King. A number of the speakers mentioned increased compliance and lower systemic adverse effects as benefits of netarsudil, but in terms -- and I don't know that we've seen much compliance data other than the higher rate of discontinuation in netarsudil.

With respect to the systemic effects on slide 67, the rates were actually the same, about 26 percent in both netarsudil and timolol. I was just questioning the conclusions made based on the data that was presented.

DR. KOPCZYNSKI: Yes. I can point out that we specifically excluded patients who had contraindications to beta blocker use, so we would

not expect to see those types of systemic effects that are in the package label and physicians are warned against.

Perhaps Dr. Mattox can talk to the benefits of once a day in terms of compliance.

DR. MATTOX: Cynthia Mattox. In treating a glaucoma patient, it's about efficacy and compliance. And having a once-a-day dosing regimen for a patient, we saw this when the prostaglandins were first introduced, how beneficial that was for our patients. Slide down, please.

The importance of that to our patients can't be underestimated. Having talked with many, many patients having to choose to do a drop once a day versus multiple dosing throughout a day is a big factor for their quality of life.

DR. CHODOSH: Marla, your turn.

DR. SULTAN: Marla Sultan. Just a question. Given the pH of netarsudil is 5 and the pH of timolol I believe is about 7, how is the blind assured in administering the drops?

DR. KOPCZYNSKI: I think we have a slide in

the core deck on comfort. It might be worth pulling that back up.

The pH of 5 does not cause any more stinging than is seen with timolol at pH 7. Slide up, please. If you look instillation site pain in this table from an adverse event perspective, it was at 19.9 percent for netarsudil dosed once daily and 21.6 percent for timolol. The buffering is very weak in our formulation, and that's what allows the drop to be comfortable because the tears will naturally neutralize the lower pH.

DR. SULTAN: Just a follow-on to that. Marla Sultan. So the netarsudil was administered at night. What was the pH of the drop that was given in the morning to that same subject?

DR. KOPCYZNSKI: It was the vehicle that was used to manufacture the drug, so it was the same pH, a pH 5. Everything was identical except there was no active ingredient in that morning dose.

DR. CHODOSH: Are there any other questions from -- oh, yes, Young?

DR. KWON: Young Kwon here. Another

question about the corneal verticillata, when the corneal verticillata was detected in the study patient taking netarsudil, was it an automatic criteria for discontinuing the medication and/or the study, or was it left up to the discretion of the treating physician to leave it up? And I ask that because as a treating physician, what would one do when one sees a corneal verticillata arise in a patient being treated with netarsudil?

DR. KOPCZYNSKI: Dr. Heah, perhaps you can address the first part of that question, and Dr. Mattox, if you'd address how do you deal with patients who have cornea verticillata.

DR. HEAH: Theresa Heah. So in our study protocol, it is up to the discretion of investigator and also subject based on any adverse event to discontinue. Upon the earlier reporting of cornea verticillata in our phase 3 studies, the investigators did discontinue the patients upon seeing it because at that time, it was unlisted as an expected adverse event in our investigator brochure.

Once we did the in vitro assay, found the cause being phospholipidosis, discussed it with our phospholipidosis expert along with sharing this information with FDA, we updated the IAB, and we discussed and actively mentioned it and presented it to all of the investigators to ensure they understand what cornea verticillata is because we want to ensure that we keep patients' safety at our utmost importance.

Dr. Mattox will talk about clinical perspective.

DR. CHODOSH: Can I interrupt you just for a minute? Can you elaborate, though? At what point did that information go out to the investigators? Because it strikes me, obviously, that affects your intend-to-treat analysis if, for example, a patient gets a few doses or a limited number of doses and then they're pulled out of the study by the examiner.

At what point in these clinical trials did that happen, and can you reflect on how that might have altered your data?

DR. HEAH: I'd like to clarify that in the intend-to-treat population, every single subject that has received at least one dose of the study drug are included in the safety analysis. So whether they're continued or not, they are still a part. As long as they received one study drug, they are part of our ITT analysis.

DR. CHODOSH: I understand that. My question is, how do you think it affected the outcome of your analysis? At what point during these three trials was there communication to the site investigators that the verticillata was not a big deal, for example, or it was something that you didn't think was going to be serious?

Because that presumably would change the behavior of investigators who, upon seeing this prior to that knowledge would be -- it looked from the data, they were pulling patients out of the study because they saw this change in the appearance of the cornea.

So when did that happen, and how might it have affected your data analysis?

DR. HEAH: First, Dr. Lewis will discuss it as well from a medical monitoring perspective. But I'd like to bring up the slide in terms of study discontinuation with cornea verticillata in terms of the time of discontinuation. We saw that upon reporting of cornea verticillata, the discontinuation rate over time did not change by days.

Can I have that slide, please, from our Aerie slide deck, please? And while we're waiting for the slide, Dr. Lewis, please.

DR. LEWIS: We became aware of the problem in the first of the trials, and I received a number of phone calls and actually had a chance to examine the patients. For all the clinicians on the panel, it looked for all the world like amiodarone did.

We then sent out notification to all the investigators, and in subsequent investigator meetings, we would show pictures and give those investigators enough heads up to understand what was to be expected.

The investigators did not necessarily all

discontinue patients. Most felt comfortable seeing the verticillata that they'd seen with the amiodarone, and for the most part, they continued their subjects in the study. It was the patients who perhaps had other adverse events, redness or something else, that might have provoked this discontinuation in the first study, but I think as things went forward, we didn't see a change.

DR. HEAH: The discontinuation rate was 3.7 percent. Slide up, please. In terms of the discontinuation by days, as you can see, the discontinuation occurred in various -- there's no specific time. So some of them -- so in conclusion, it did not affect our per-protocol efficacy analysis.

DR. CHODOSH: Did you want to say something more before we go to the next question?

(Dr. Kopczynski gestures no.)

DR. CHODOSH: Marla?

DR. SULTAN: Marla Sultan. That's a great breakout. Do you actually have it broken out for each AE? I think that slide you just had up had

corneal verticillata, hemorrhage, and I forget the third altogether.

Did you break it down by days discontinued, and do you also have a subsequent or a complementary slide, which has the numbers of patients that remained within the trial that have those adverse events reported but not reported and discontinued?

DR. KOPCZYNSKI: Dr. Heah?

DR. HEAH: Thank you for the various questions. Can you repeat your questions so that I can answer every single question?

DR. SULTAN: Sure. That last slide that you just called up, do you have that broken out for each AE as opposed to all three lumped together?

DR. HEAH: Yes. That was specifically for cornea verticillata. So let's look at conjunctival hyperemia. Slide up, please. This is discontinuation in terms of by days for conjunctival hyperemia. As I mentioned earlier, the incidence of pooled data from four phase 3s, 54.4 percent. From two phase 3s was 57 percent,

and that's the discontinuation by days.

Next slide up, please. Conjunctival hemorrhage by days of discontinuation, so 17.2 percent incidence, discontinuation was 1 percent. This is the breakdown of the conjunctival hemorrhage discontinuation by the day.

DR. SULTAN: The latter part of my question was, do you have -- these AEs can be reported, and the patient yet remains within the study. Do you have that complementary information?

DR. HEAH: Reported but remain in the study.

DR. SULTAN: What you showed was the reporting of --

DR. HEAH: The discontinuation --

DR. SULTAN: -- AE and the discontinuation, but the AE could be reported, but the patient remains within the trial.

DR. HEAH: Thank you very much for that question. For cornea verticillata, slide up, please. This is from our CS304 study. To your question, upon continued dosing, we have information as well.

If you focus on the top part of this busy slide on the study eye, you can see that with no drop withdrawal, there are two patients that did resolve the cornea verticillata while still being dosed with netarsudil QD.

DR. SULTAN: Only two subjects remained throughout the trial with verticillata?

DR. HEAH: Two subjects from the CS304 study, yes, basically continued with no drug withdrawal and had resolution of the cornea verticillata.

In terms of hyperemia, let's go back to my core slide on the discontinuation rate. I think to your question -- discontinuation core slide, please. Slide up, please, 77. Just to clarify, 6 percent of the patients discontinued due to hyperemia, which means the rest remain in the trial; 3.7 percent discontinued due to cornea verticillata; 1 percent with conjunctival hemorrhage.

I hope I'm answering your question, Dr. Sultan, because the rest of them remained in

the trial and did not discontinue from the trial or study drug.

DR. SULTAN: So maybe I'm not understanding the answer, but not what I intended for my question.

DR. HEAH: Okay.

DR. SULTAN: My question is, if a patient was -- sorry, it's so awkward. If the patient was noted to have conjunctival hyperemia reported as an AE, but the patient stayed within the trial, how many of those patients stayed in trial even with the reporting of an AE of hyperemia as opposed to hyperemia was noticed, reported as an AE, and that patient was discontinued because of that finding of an AE?

So how many people stayed with hyperemia all the way through?

DR. HEAH: Slide up, please. So of the 839 subjects, 49 subjects discontinued from the trial due to hyperemia. So the remaining of the patients stayed in the trial.

DR. SULTAN: But the other 790 -- I don't

know -- I give up on my math. But 700 and something patients did not all also have hyperemia, right, or did they?

DR. HEAH: Right. They did not. The 839 minus 49, so 790 patients remained in the trial, but they don't discontinue due to hyperemia.

Just to clarify again, in our case report form, patients can discontinue due to an adverse event. But if they have concurrent adverse event at that time of discontinuation, they are also counted, they are reported in the trial. So they could be having conjunctival hyperemia and hemorrhage and discontinue because, say, for example, due to hyperemia but also have that concurrent AE, yes.

DR. SULTAN: What is that concurrent AE rate?

DR. HEAH: Could I have the slide on concurrent AEs, please? Thank you. I'm glad I got that.

DR. SULTAN: Yes.

DR. HEAH: Concurrent AEs, please. Slide

up. Concurrent AEs with hyperemia, for example, those with cornea verticillata and conjunctival hyperemia, is 11.8 percent. Hyperemia and hemorrhage, 9 percent; hyperemia and vision blurred, 4.8 and 1.9. But that doesn't mean that they discontinued. They report hyperemia at the same time.

DR. CHODOSH: We're going to take I think two more questions. Randy, you're next. State your name.

DR. HAWKINS: Randy Hawkins. Sorry if it's clear to everybody else. I actually need a little bit of clarification. It may have happened because I wasn't listening clear enough when the statistician from the FDA reported.

Based on the drug netarsudil being given once daily and the requested indication, is the drug inferior or not inferior to timolol? Is it just as effective? I got thrown off by the presentation above 25. I don't know if you need to just throw the information away or not. I'm sorry if I'm the only one confused by that.

DR. CHODOSH: It's a fair question.

DR. CHAMBERS: This is Wiley Chambers. I think there is no disagreement that the drug and timolol are equivalent in IOP lowering for less than 25. There is a general -- what's generally been presented is that there is more IOP lowering in timolol at higher intraocular pressures, so that when you go above 25, timolol has generally been shown to have a little bit more IOP lowering than netarsudil does when you're above 25.

We have not generally done -- what is not inferior apparently depends on where you are as far as IOP lowering.

DR. HAWKINS: Thank you. Very helpful.

DR. CHODOSH: Did you have one more question?

DR. KWON: Yes. This goes back to the corneal verticillata question. This is Young Kwon here again. As a clinician, I got the sense, listening to the panel -- from the sponsor, that corneal verticillata is not necessarily a contraindication to continuing to use the

medication if the patient can tolerate it since it doesn't seem to impair the function.

Did I hear that correctly? Because my experience with corneal verticillata, say from amiodarone, is you continuing using it because it's a lifesaving drug, but can you say the same thing for netarsudil? We do have other glaucoma medications we can use when we see corneal verticillata. What is your opinion on that?

DR. KOPCZYNSKI: Yes, we do not see verticillata as a reason to discontinue or not to use the drug, but I'd like Dr. Serle and Dr. Mattox maybe to give their perspective as clinicians.

DR. MATTOX: As a clinician and all of us who are here who are ophthalmologists have seen amiodarone corneal verticillata, and generally, amiodarone corneal verticillata, to the stage or the grading, if you will, is typically much higher and occurs in almost a hundred percent of patients. In fact, oftentimes, we see it. The patient is completely unaware of it. We have to point it out to them because there are no visual complaints.

What I've seen from the sponsor is that this doesn't occur in everyone through the trials. The grading is mild, and these patients also did not have complaints. Again, trading off the risk of serious irreversible blindness from glaucoma compared to what we're seeing from the corneal verticillata, I think clinically the risk is acceptable.

DR. SERLE: You've asked about options. Dr. Mattox has covered the views of those who see patients with amiodarone as well as looking at the data from the study, that the drug does not interfere with vision, and vision is what we're trying to preserve in our patients. As we all know, lowering IOP is what preserves vision in glaucoma patients.

We do have other options, but I think we've reviewed some of the limitations of those. First of all, not every drug works in every patient, and we all know that we cannot yet get adequate IOP control in our patients.

Could you bring up the slide with the

surgery graph? I think it's the first one. I think we'll know we're there with glaucoma when we no longer have to operate on any of our patients and when we don't have patients going blind, and we're not there yet.

The last time we had any reduction in the number of surgical volumes was around 1995-1996 when the three classes of compounds were introduced for clinical use. It's my hope, if netarsudil gets approved, we'll have another reduction in incisional surgical volume in this country.

Now, the numbers here are only the Medicare patients, so there are a lot, many more patients that we're doing glaucoma surgery on. So I think this kind of information proves we're not there yet. We certainly need other options. We don't have a sufficient number.

DR. CHODOSH: Thank you so much.

We're going to break for lunch. We're going to reconvene at 12:30 sharp. It's my understanding that you don't have to remove your personal belongings, but you can if you want. Committee

members, please, no discussion of the meeting during lunch among yourselves, with the press, or any member of the audience.

Thank you. We're adjourned.

(Whereupon, at 11:36 a.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(12:29 p.m.)

Clarifying Questions (continued)

DR. CHODOSH: The next thing on the agenda today is an open public hearing. As far as I know, no one's signed up to speak. So before I go through the long introduction to the open public hearing, is there anyone in the audience who intended to speak? I'll wait till these folks come in.

Again, this is the time for the open public hearing. Is there anyone in today's audience who wanted to address the committee or speak?

(No response.)

DR. CHODOSH: Not seeing that, I think we're going to move forward. What I would like to do, before we go to the next section, is to see if there was any more discussion questions for either the applicant or to the FDA from our committee. I particularly liked the specificity of the questions as we got farther into the morning, and I thought it was productive for us to hear the harder

questioning. I think it's good to flesh these things out. Better to do it here than later afterwards to say, oh, I should have asked.

I wanted first to put forwards to the committee that if anyone had any questions either for the applicant or for the FDA, that this would be the time to do that, because following this, we're going to move to the questions.

Yes, Marla?

DR. SULTAN: Marla Sultan. Just a question, I think this is an okay question. But I was just wondering if this application has already been submitted to other parts of the world, and if that is so, if there was any feedback from those interactions that is publicly shareable.

DR. KOPCZYNSKI: It has not been submitted elsewhere.

DR. CHODOSH: Geoff first. State your name.

DR. EMERSON: Geoffrey Emerson, a question for FDA about the draft of the FDA label in our briefing packets. Is this a fine time to ask that?

DR. CHAMBERS: Wiley Chambers. So as part

of the original application, applicants are required to submit a potential label, a whole series of labeling, and the FDA frequently makes comments about that, and there is give and take back and forth as the application proceeds. Most of that generally occurs toward the later stages of the application.

We had not shared the particular comments that you have seen with the applicant prior to it appearing in the briefing document, but it was meant to initiate discussion both at the advisory committee and in the future with the applicant.

So you should feel free to make any comments that you have with either things that were in there originally, or things that were struck out, or things that should be added.

DR. CHODOSH: Wiley, during the question session, there's an opportunity to talk about labeling, right? Is that the better time to do that, or should we be engaging in that now? Are we putting the cart before the horse?

DR. CHAMBERS: At this point, I would ask

questions. If you have questions about it, do that now. As far as what your recommendations and suggestions are, do that at the time we have the questions.

DR. CHODOSH: Did you want to follow up on that, Geoff?

DR. EMERSON: Yes. Then I'll ask my question. It's section number 14 in the FDA label on clinical studies. It looks like the FDA has proposed adding the phrase "in patients with baseline IOP of less than 25 millimeters mercury."

My question for FDA is, with this added, does that mean that if a doctor's treating a patient and their baseline IOP is more than 25, are they using the medication off label?

DR. CHAMBERS: Whether a product is used on or off label depends on what is listed in the indication section, not what is listed in the clinical trials section. The clinical trials section is designed to give you more information about what was done, not to limit the use of the product.

DR. CHODOSH: Young, you had a question?

DR. KWON: Young Kwon. This is more of a scientific curiosity for the sponsor, and that is, if netarsudil works directly at the level of the trabecular meshwork, why does it seem pressure independent, at least in one of the slides that you show, when it reduces the pressure with a baseline IOP of less than 25 or over 25?

Do you see what I'm trying to say? The trabecular meshwork, we're all taught, is to be sort of a pressure-dependent component of the outflow facility. So I was just curious.

DR. KOPCZYNSKI: I can certainly share how we think about that. Slide up, please, just to start with a slide that references what you were pointing to, which is that baseline pressures above 25 as well as below 25 really have got very similar IOP lowering with netarsudil, and that differs from timolol, which got slightly larger IOP reductions in greater than 25.

We have, we believe, multiple mechanisms of action, and we focus primarily on the trabecular

meshwork. It's the one that seems to be the predominant IOP-lowering mechanism. We do have data that suggests it may also lower episcleral venous pressure.

If you think about when pressures get lower, the influence of the pressure in the episcleral veins becomes predominant. If an individual has 10 millimeters of episcleral venous pressure and a total intraocular pressure of 16, then the episcleral venous pressure is actually the majority of that pressure in the eye.

If we can lower episcleral venous pressure, we actually are lowering the floor in terms of the IOP reductions that can be achieved with our drug. So we think that's part of the explanation for why our drug continues to maintain the same IOP lowering as we get to lower pressures.

If I could bring up one more slide to speak to that, slide E-46, please. The slide I'm pulling up is a responder analysis that we conducted on the pooled data from the three different efficacy studies. We're looking at the different

populations, starting from the right, the population of patients with pressures less than 27, and looking at the percentage of patients who achieved at least a 20 percent IOP reduction.

You can see as we move to the left with lower baseline IOPs, the percentage of patients who were actually able to maintain that 20 percent or greater actually increases with netarsudil and decreases with timolol. Eventually, there's a statistically significant difference at baselines less than 23 and less than 22.

We're still learning about this drug. We think it's very interesting, from a number of different perspectives, to have this new mechanism of action and what appears to be a combination of mechanisms of action to take into the clinic. But this is certainly part of the reason we think we are able to maintain that efficacy lowering even as pressures get lower.

DR. CHODOSH: I had a scientific question. James Chodosh. So ROCK inhibitors have been proposed to treat corneal endothelial dysfunction,

and I was looking maybe with a more sharper eye, not being a glaucoma specialist, at that component. Would this study have been powered sufficiently to detect preservation of endothelial cell count in patients who received that versus timolol?

DR. KOPCZYNSKI: I think we would have to have started it with some kind of injury to see what has been reported for the Rho-kinase inhibitors.

To your point, it's been shown, certainly preclinically, that if you scar the corneal endothelium and then treat, say, a monkey with a Rho-kinase inhibitor, it actually accelerates the healing of that tissue and allows actually repopulation of that scarred area more rapidly than if the monkey is not treated with a Rho-kinase inhibitor. It is a very interesting and active area of research.

DR. CHODOSH: Are there any other questions from the committee?

I'm sorry. Peter?

DR. ZLOTY: Peter Zloty. We looked at

hyperemia as being one of the adverse effects. Was there any increase in cell and flare? And in that regard, would there be any reason to discontinue this before a planned surgery like a cataract surgery? I ask one of the participants who has a lot of clinical expertise in answering this, please.

DR. KOPCZYNSKI: Theresa and maybe Rick as well.

DR. HEAH: I'll answer the first part on the cell and flare. Slide up, please. We collected the anterior chamber cell count looking at cells and flare in our biomicroscopy slit-lamp measurements, and we didn't see any clinical differences here between netarsudil QD and timolol BID.

DR. LEWIS: Speaking as medical monitor for the trial -- this is Rick Lewis, medical monitor for the trial -- there was no concern from the investigators, and some of the subjects did, in fact, have surgery with no adverse events reported from that.

Questions to the Committee and Discussion

DR. CHODOSH: Thank you so much. Those were good questions.

Bear with me as I go through this. We're going to be using an electronic voting system for this meeting, and for those of you with microphones, you'll see that there's a "yes," "no," and "abstain" on your microphone base.

Once we begin the vote, buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. This is not a situation where you vote often. If you're unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. So if you have voting rage, you can keep pressing your button.

(Laughter.)

DR. CHODOSH: After everyone has completed their vote, the vote will be locked in. That's when it stops flashing. The vote will then be displayed on the screen, and the DFO will read the

vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. So please, vote and state your vote consistently, or it will create confusion. We're going to continue in the same manner through the questions.

I'm going to read the first question, and then we're going to have a discussion, for those on the committee, about the wording of the question so that everyone understands the question before we vote on it. If there's no concerns or if it's clear, then we can move to the next question.

The first question is, do the clinical trials support the efficacy of netarsudil ophthalmic solution for reducing intraocular pressure in patients with open-angle glaucoma or ocular hypertension?

We don't want to hear your vote. We just want to know whether this question is ambiguous, or you want clarification, or have any questions or comments about the question, those of you who are

voting members?

(No response.)

DR. CHODOSH: I didn't say, "If no, what additional trials would you recommend," but we're going to go ahead and vote on this question. Again, "Do the clinical trials support the efficacy of netarsudil ophthalmic solution for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension?"

Please vote. I think this goes on for 20 seconds or something like that.

(Voting.)

DR. CHODOSH: Commander Bonner is going to take over for me.

CDR BONNER: For question number 1, 10 yes, zero no, zero abstain.

DR. CHODOSH: That makes moot the subpart of the question.

The second question, does the efficacy -- oh, everybody has to state their name and vote. Thank you. Sorry. Beginner's misluck.

We're going to around the table of the

voting members -- David, we'll start with you -- and you should state your name and state your vote. You can state why you voted that way or not, or if you have any other comments.

DR. YOO: David Yoo. Question 1, voted yes. No other comments.

DR. GICHERU: Sidney Gicheru. Voted yes. No further comments.

DR. KING: Tonya King. Voted yes, and I believe it's for a subset of the patients.

DR. CHAMBERS: Dr. Chodosh, can I ask if you think it's for a subset of patients, can you explain what subset, for administrative record for me, please?

DR. KING: Yes. Tonya King. I believe the evidence for less than 25 baseline level is convincing. That's what I based my vote on.

MS. DeLUCA: Jo Ellen DeLuca, patient representative. Yes.

DR. HAWKINS: Randy Hawkins. Voted yes.

DR. ZLOTY: Peter Zloty. Voted yes. I think this is an adjunctive medicine and would

suggest we talk about that with the labeling.

DR. CHODOSH: James Chodosh. Unqualified yes.

DR. OLIVIER: Mildred Olivier. Yes, and I also based it on ocular hypertensives who might have pressures of 26 and below and open-angle glaucoma.

DR. KWON: This is Young Kwon. Voted yes. No other comments.

DR. EMERSON: Geoff Emerson. Voted yes. No comments.

DR. CHODOSH: The comments that I heard from Dr. King was that for patients, the evidence is there for patients less than 25 millimeters of mercury at starting pressure. I heard from Peter Zloty that it should be considered an adjunctive medication. And that was it, right?

Oh, Mildred Olivier, what was your comment?

DR. OLIVIER: Oh, just similar to [inaudible - off mic].

DR. CHODOSH: Dr. Olivier echoed Tonya King's comment.

Question 2, does the efficacy of netarsudil ophthalmic solution demonstrated in the clinical trials outweigh the safety risks identified for the drug product? For the committee, are there questions about wording, meaning, intent of this question that you'd like to discuss or ask about?

(No response.)

DR. CHODOSH: I don't see any, so we're going to proceed to vote. Does the efficacy of netarsudil ophthalmic solution demonstrated in clinical trials outweigh the safety risks identified for the drug product?

(Voting.)

CDR BONNER: For vote question 2, 9 yes, 1 no, zero abstain.

DR. CHODOSH: We're going to go around the table. Please state your name and your vote, and elaborate as you would, please.

DR. YOO: This is David Yoo. For question 2, I voted yes, and I believe that it seems the efficacy does outweigh the adverse events and side effects.

DR. GICHERU: Sid Gicheru. For question 2, I voted yes. No further comments.

DR. KING: Tonya King. For question 2, I voted no. Although the sponsor seemed to adequately discuss the severity of the adverse events, it seemed to me the high discontinuation rate was still a concern.

MS. DeLUCA: Jo Ellen DeLuca. I voted yes. It appeared to be a good thing for the patient.

DR. HAWKINS: Randy Hawkins. I voted yes. I also had some concerns about the rate of adverse.

DR. ZLOTY: Peter Zloty. I voted yes. No other comment.

DR. CHODOSH: James Chodosh. I voted yes. I think when looked at in the context of other available intraocular pressure-reducing medicines, this to me fits right in the middle, so I had no concern. Obviously, always concerns about side effects, but not relative to the question.

DR. OLIVIER: Mildred Olivier, voted yes, and very similar comments about adverse events with other drugs on the market.

DR. KWON: This is Young Kwon. I voted yes. Just a comment. Despite the higher rate of side effects and discontinuation rate, this represents a major advance in glaucoma therapy because it represents the first in a new class of glaucoma medications, and therefore my vote of yes.

DR. EMERSON: Geoff Emerson. I voted yes. I agree this being the first in class makes it valuable as well as the QD dosing, and I feel the side effects are manageable.

DR. CHODOSH: So because we have a no vote, I get to ask Dr. King, what additional trials would you recommend?

DR. KING: I guess a safe answer to that would be longer duration trials where maybe the continued extent of follow-up could look more closely at these side effects that have been identified. Possibly even, as was discussed as some of them ended up with further observation, being determined not to be of high concern, that going forward, a longer study could look at that more closely.

DR. CHODOSH: I'd like to ask the FDA. What's the status of post-approval monitoring for a drug like this, and what might the FDA request or what might we expect if we have a concern about side effects of the drug?

What I heard from the committee, everyone said yes, that the drug appears to be effective and they recommended approval, but there were some concerns about the side effects. So how does the FDA address that after approval, assuming that they did approve it?

DR. CHAMBERS: The FDA has a range of possibilities. The agency can require premarket additional trials to be done. It can require a post-market safety trial, and there is no limitation to what that trial can consist of; and because it's a safety issue, it can be required of the particular product.

The other option is to go to what is routine monitoring. So even if we added nothing in addition, routine monitoring would require the company to collect all adverse events that are

seen, depending on whether they are serious and unlabeled, reporting it as relatively quickly. Even routine monitoring, even if it's not serious or unexpected, comes in quarterly in the first two years, then semiannually, and then annually afterward for the life of the product that's marketed.

Labels are not static. We continue to follow what goes on, and labeling will change as we learn new things. We do not anticipate that we know everything about a particular product at the time of approval.

DR. CHODOSH: Thank you for that clarification.

This is the point in time at which I believe we're supposed to discuss suggestions concerning the proposed draft labeling of the product. Does anyone on the panel have specific suggestions relative to the documents you reviewed about labeling? Marla, please state your name.

DR. SULTAN: Marla Sultan. I actually have a question before a recommendation. I noticed on

the adverse reactions, on the first page of the label, only conjunctival hyperemia at 54 percent is listed. And I was just wondering if there should be additions there for anything above 5 percent that's been noted or if you just list the highest adverse reaction.

DR. CHAMBERS: This is Wiley Chambers. Are you talking about the highlights at the top?

DR. SULTAN: Yes, the highlights.

DR. CHAMBERS: The highlights are designed just to give you a quick overview of the major events that are there. They do not routinely list all adverse events, but any of those of special significance or of high frequency is what would get listed there. There is no automatic limitation or automatic listing.

DR. SULTAN: Am I'm allowed to make a recommendation or just put something out there for thought? Maybe corneal verticillata should be highlighted there because although a lot of good information about its resolution has been shared by the company, it might be something that would be

shocking to the physician when it first appears. So it would be important for them to -- as well as the patient, should be mentioned for that to be highlighted.

DR. CHODOSH: I have a follow-up to that also because I was thinking about the verticillata. The guidance in amiodarone deposition is, in my experience, patients don't know they have it. It doesn't seem to affect their vision, and I teach ignore it. It's a sign that you can tell the patient's on the drug even when they've forgotten. So it benefits you.

The question then, though, is to what degree does the labeling provide guidance to physicians who are caring for patients on this drug to whether or not they should ignore it, report it, or consider stopping the medicine? Will there be guidance in the labeling to the caring physician as to what to do about it when they see it?

DR. CHAMBERS: This is Wiley Chambers. To the extent that we believe the physician can be further educated or should be further

educated -- not can be, but should be further educated in what to do -- those are statements that we would commonly put in a package insert.

There is a separate section toward the end of things that we believe the physician should communicate to patients, and those recommendations are also fair game.

DR. CHODOSH: This is James Chodosh again. Is it the intent of the FDA then to be specific and tell physicians that the drug does not need to be discontinued? Is it the intent of the FDA, if this goes forward, to tell physicians they should report it? I don't recall actually what I read with regard in the document, but maybe you can help us.

DR. CHAMBERS: Wiley Chambers. One of the purposes of this advisory committee meeting is to get your feedback on what you think we should do.

DR. GICHERU: Sid Gicheru. As a practicing physician, I think we should leave some of that to the physician's clinical judgment, but I do think mentioning corneal verticillata would be important.

DR. CHODOSH: As a corneal specialist, I

will be getting these patients in referral, particularly if there's no guidance in the labeling. This sort of comes back to the hyperemia issue but also this corneal change, because it looks to me like it gets better with time off the medicine. But what I was wondering during the data presentation is what will it look like after a year or use, or 2 years, or 10 years of use, and how will that change the cornea?

That was again part of my question of post-approval monitoring and how would we know. I know these things -- physicians frequently look for things to write about, and so there will be case series written about it probably and what comes of it. But I'm interested in having it be a formal process so that we can really learn about it.

My experience with amiodarone is that it gets to a certain point and it stops. It's there, but it doesn't continually worsen. The whole cornea doesn't become one dense spiderweb of verticillata, but in this case, we don't really know what the long-term outcome is.

I'm just wondering -- I'm asking the question, not answering your question, Dr. Chambers, but asking the question, what should we do? And I'm curious as to what the rest of the committee thinks.

Should we recommend is that the FDA -- that the physician need not worry about it? Should we recommend to the FDA that the label say please report it by some of the mechanisms that was done, or should we recommend that patients be considered to stop it? I don't hear a big enthusiasm for the latest option, but I think they're all on the table.

Randy.

DR. HAWKINS: Randy Hawkins. So for a non-ophthalmologist, I'd probably defer to the ophthalmologist specialist. Is this something that's very, very well known, the entity? It seems like it's a known entity, maybe not in this category.

Some elevation that it's there and to keep your eyes open so that there's knowledge about the

natural history of this occurrence in this new drug. It'd be valuable.

DR. ZLOTY: Peter Zloty. I practice in a somewhat rural/suburban setting, and I've been called to the emergency room to see corneal verticillata that they thought was acute herpetic keratitis. I've had patients who've been treated for weeks with topical Viroptic for corneal verticillata.

It's not well known by the optometric community, which will be prescribing this as they do other glaucoma drops. It should be clear on the package insert and on the bottle that this is a known, perhaps inconsequential, however we want to word it, non-visually significant side effect for education purposes.

DR. CHODOSH: James Chodosh. I have a set of slides in my slide set where a patient with amiodarone deposition was repeatedly scraped for their thought-to-be herpetic keratitis, inducing scarring in one eye, and the answer was clearly in the other eye. Two years of observation without

any antivirals elicited no herpetic episodes.

So I think you're right, and that's very important. My question was really can we rely on the amiodarone evidence with this new drug -- I'm a big believer in the unintended consequences and the things we don't know, we don't know. And I'm not against this drug or this class of drugs at all, and I'm not bothered by the depositions, personally. But I'm just wondering, again, to say it again, what should we tell the physician?

Since this is a new class of drugs, should there be some slightly higher monitoring of this particular aspect of it so that we have a good way to learn what the natural history is, and then in an amended insert, perhaps two years down the road, it becomes a non-issue. That's really all I'm after rather than have it be out there and be a concern.

Yes, Dave?

DR. YOO: Dave Yoo. When you guys approved the prostaglandins and then you found out that they had lashes elongating and the pigmentation

alteration, what was the process then?

DR. CHAMBERS: Wiley Chambers. The prostaglandin analogues originally all had post-marketing study commitments to do at least five years of monitoring to determine whether the increase in pigmentation was of any particular consequence.

DR. YOO: Then to me, that seems like --

DR. CHAMBERS: The labels then were all modified after that point in time.

DR. YOO: If you're telling us that the labels can be modified, that seems like that would be reasonable to me, especially because we don't know what the long-term consequence is going to be, if it is going to become more severe in terms of the verticillata.

DR. CHODOSH: James Chodosh. So another question to the FDA, which is forgetting about intraocular pressure reducing drugs, when the FDA sees a new class of drugs, given by whatever means, does that typically lead to some heightened level of post-approval monitoring above baseline?

DR. CHAMBERS: This is Wiley Chambers. The short answer is that every drug is evaluated on its own individual basis. There is not an automatic anything except that there is a requirement to collect all adverse events that occur, and we routinely monitor every approved product and both proposed and company's proposed changes to the labeling as we learn new information. It is an ongoing process, and we can intend for it to continue to be an ongoing process.

DR. CHODOSH: James Chodosh. Geoff, we're going to come to you in a moment. I wanted to give the applicant a chance -- I'd like to hear maybe Dr. Lewis tell us what you think about this in hearing that concerns --

I've been overruled.

(Laughter.)

DR. CHODOSH: And I've learned when the government overrules you, you should listen. Sorry.

Geoff, we're going to go to you.

DR. EMERSON: I'm looking at section 6.1,

which is the top of page 65 in our briefing materials. And listed as the most common adverse reactions, it lists instillation site pain. This is put in by the applicant and not by the FDA. I'm noticing that instillation site pain was actually lower for the netarsudil at both the QD and the BID dosing as compared to timolol, so I'm wondering if it needs to be in there.

I guess what I'm wondering is it in the label for timolol. If so, then I could see why you'd have it in this label as well. But if it's not in the timolol label, then I wouldn't see a need to have that because I think a certain number of our patients, the eye drop hurts no matter what it is, kind of like muscles hurt after exercise.

DR. CHAMBERS: This is Wiley Chambers. Again, if you have a particular recommendation, just please make the recommendations, and we will consider those as we go along.

DR. EMERSON: Geoff Emerson. My recommendation is if instillation site pain is not part of the timolol label, then I would strike that

from 6.1.

DR. CHODOSH: I would recommend that there be something to the effect that use is recommended at once a day and that using it more than that will increase the incidence of side effects. I know of physicians who go beyond the recommended doses of drugs. Clearly with a beta blocker, that can have an effect. Although this is not expected to have systemic effects, we saw in the BID study that there was a substantial increase in side effects. So that would be my recommendation.

DR. KWON: Young Kwon. This is on a different topic, but in the labeling section 11 under description, it says, "Netarsudil is Rho-kinase and norepinephrine transporter inhibitor."

That part has not been crossed out, as was the case in section 1 earlier and on page 63. So I'm not actually sure why it was crossed out in the first place. I think it was the FDA's decision to do that, but if you're going to do that, then you should try to be consistent.

DR. CHODOSH: This is James Chodosh. I think that was a source of confusion for many of us. The mechanism is the mechanism, and put it or don't, but it should just be consistent.

DR. KWON: I have a second comment. Young Kwon again. In section 12.2 in pharmacokinetics, it states, "In a clinical study of Rhopressa dosed once daily in the morning," and the way the sponsor has proposed for this drug to be used is in the evening. So I was wondering if this was the wrong wording or it was based on the earlier study where they actually studied in the morning and at night and decided to put that specifically. It was a point of confusion for me.

DR. CHAMBERS: This is Wiley Chambers. As I pointed out, whether things are on label or off label is how it's written in the indications and/or the directions section. There are other sections in the label that just describe what was done. So in this particular case, this is a description of the trial that was done, just as the clinical trial section is our descriptions of what was done, not

necessarily what is recommended.

DR. CHODOSH: We had a question from Marla.

DR. SULTAN: A comment --

DR. CHODOSH: Say your name.

DR. SULTAN: Marla Sultan. In section 6.1 in the adverse reaction section, I noticed -- actually, I had made a similar comment earlier -- there's a specific percent given for one adverse reaction, and then the others were just lumped in as greater than 10 percent or 5 to 10 percent. I think it might be helpful to have the percentages from the trials listed more specifically instead of just greater than 10 percent.

My second comment is in that section 12.3 under the pharmacokinetics, I don't know if this is available, but it would be interesting to know the peak concentration, which is not noted there.

DR. CHODOSH: Any reply?

DR. CHAMBERS: Again, we will go through all various comments that you make during this, as well as we will have further discussions with the

applicant as we make determinations on the approvability of the application. We appreciate any comments that you make at this point in time.

MS. DeLUCA: Jo Ellen DeLuca, patient representative. I'd like to have something that feels more positive. I think sometimes the labeling gets to be so negative from the start that it makes people look for something that's really wrong. I think that that would denote the FDA cares as well, which they do, and the public does not always see that point.

DR. CHODOSH: I think I see all the clinicians in the room sort of smiling because we all have our patients who come and say, "This drug you gave me can do all these horrible things," and the labeling can really freak people out. I try not to read it myself.

(Laughter.)

DR. CHODOSH: Young?

DR. KWON: Young Kwon here. In section 14 under clinical studies, this is more of a question. It states on the third line there, "In the evening

had a mean baseline IOP of 21 to 22 millimeters of mercury," and the next part is crossed out, "and demonstrated up to 5 millimeters of mercury."

I was wondering how the 21 to 22 millimeters of mercury was chosen, and I couldn't find a specific reference for that. The graph that I was looking at, at page 31 of the briefing material, at least on the bottom graph, if anything, was between 22 and 23 as opposed to 21 and 22. So it's just a small -- I was wondering where that range of numbers came from.

DR. CHAMBERS: Wiley Chambers. We will go back and check the numbers, but I suspect that this was a reference to the subset of patients from the two trials. And the reason for the range was that there wasn't a single trial. It was more than one trial.

We also generally tend to round some of these numbers. We commonly measure intraocular pressure on an instrument that is in 2-millimeter increments. When we start getting into tenths of millimeters, I certainly question the relevance of

being that specific.

DR. KWON: Just a reply to that, if you refer to the entire population studied on, say, 302, then the entire population mean intraocular pressure at the baseline was somewhere between 22 and 23 is what I was looking at.

DR. CHAMBERS: This is Wiley Chambers. Again, we will go back and check numbers.

DR. CHODOSH: Marla, I believe you still had another question.

DR. SULTAN: Yes. Just a question. I noticed in 12.3 in the pharmacokinetics section under metabolism --

DR. CHODOSH: A little bit louder, closer.

DR. SULTAN: I'm sorry. Marla Sultan. Just noticing in 12.3 in pharmacokinetics, in the metabolism section, there are a couple of comments about in vitro metabolism. If there is in vivo information available, it might be helpful to put that there. Also, it speaks to exposure, what happens, how the active metabolite is produced, but it doesn't speak to what happens to the active

metabolite. That might be helpful to add.

DR. CHAMBERS: This is Wiley Chambers. We'll go back and consider it, but if it doesn't have an impact on the physician's decisions to use or not use the product or the patient's decision to use or not use the product, we don't always include it.

DR. CHODOSH: Mildred?

DR. OLIVIER: Mildred Olivier. I don't know if this is the -- does this class of medication have a different color top to it, or do we know?

DR. CHAMBERS: This is Wiley Chambers. So for those of you that do not know, the American Academy of Ophthalmology has a recommended color cap for a number of different ophthalmic medications, not all medications. Most of the IOP-lowering medications do have different caps to help minimize confusion between them.

The process for determining colors on caps are requests made to the American Academy of Ophthalmology, who then makes recommendations and changes -- well, there is a committee that goes and

reviews that and makes recommendations to the board. And ultimately, if the academy decides to change its recommendations on cap colors, the FDA has generally been following those recommendations.

DR. CHODOSH: This is James Chodosh. We're going to run out of colors pretty quick, I think. If you guys keep inventing new classes of drugs, we have a big problem. But I'm saying that facetiously.

We're going to go back to Marla, who I think I had another follow-up.

DR. SULTAN: It was just a follow-on. When I asked about the metabolite, possibly adding that information about excretion or where it goes, it just relates to the fact that this is not studied in pregnant or nursing women. A physician may think about things differently depending upon where the metabolite's going, how it's being excreted, and things that we haven't even discussed here today or don't come up in the general population. That's why I thought that might be value to that type of addition, but her color cap is much more

important.

DR. CHAMBERS: This is Wiley Chambers. Thank you very much.

DR. CHODOSH: Does the committee have any other questions for the FDA?

DR. KWON: Young Kwon here. One more question. As a follow-up to the pregnant women, would there be any statement on the labeling on use on the pediatric population, under the age of 18?

DR. CHAMBERS: At the present time, the expectation is that because the product has not been studied in a significant number of patients under the age of 18, that the label is likely to say that safety and efficacy has not been established. So not either saying you can use it or can't use it but say the state of the fact, that it hasn't been established.

As a general policy, the agency has encouraged studies to be done in pediatric patients unless the product qualifies for one of the various waivers. One of the waivers is if the product does not provide a meaningful benefit and is not likely

to be used in a substantial number of children. Glaucoma does not have a large pediatric population. Don't take that as they're not as significant and there are not patients; there absolutely are. But it is a relatively low population.

You saw in the applicant's statements, the agency encouraged original trials, and it encouraged the applicant to attempt to study it in pediatric patients. And the agency will continue to encourage the applicant to study it in pediatric populations so that the labeling can be informed by that. But I'm not sure that there is a particular mechanism to require that as this point in time.

DR. CHODOSH: Thank you. Are there any comments before we adjourn from the FDA itself, outside of what we've discussed?

(No response.)

DR. CHAMBERS: Not seeing anything else from my colleagues, I would like to take the opportunity to thank all of you for your time and consideration of this application and the time for coming to the

meeting. And I would also like to thank the applicant for bringing forward the application.

Adjournment

DR. CHODOSH: I'd also like to thank my colleagues on the committee for doing such a great job and for taking the time to do this with me, and those folks from the FDA did a great job, and also thank the applicant for what I thought was a very clear presentation.

We're going to adjourn. I'm supposed to tell the panel members to take all your personal belongings with you as the room is cleaned at the end of today, and they may not be here if you forget them. If you wish materials to be disposed of, you can leave them on the table, and they will be shredded carefully, and if you would drop your name badge off at the registration table so that they can be recycled. We will now consider this meeting adjourned. Thank you very much.

(Whereupon, at 1:23 p.m., the meeting was adjourned.)