

1

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
UNITED STATES FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

Dermatologic and Ophthalmic Drugs

Advisory Committee

Session 2

Friday, December 5, 2008

11:50 a.m.

Hilton Washington, D.C./Rockville  
Rockville, Maryland

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

C O N T E N T S

|   |      |
|---|------|
|   | 2    |
|   | Page |
| Afternoon Opening Remarks and Introductions,<br>Michael X. Repka, M.D.  | 4    |
| Conflict of Interest Statement,<br>Yvette W. Waples, Pharm.D.   | 7    |
| Industry Presentation:  |      |
| Introduction and Overview,<br>Scott Whitcup, M.D.   | 10   |
| Clinical Overview,<br>Frederick Beddingfield, M.D.  | 17   |
| Safety Overview,<br>Sef Kurstjens, M.D.   | 35   |
| Questions/Clarifications  | 48   |
| FDA Presentation:   |      |
| Division of Anti-Infective and Ophthalmology<br>Products: Advisory Committee Meeting<br>for Bimatoprost Ophthalmic Solution for<br>the Treatment of Hypotrichosis of the<br>Eyelashes, Rhea Lloyd, M.D. | 71   |
| Questions/Clarifications  | 87   |
| Open Public Hearing:  |      |
| Brandel France De Bravo,<br>National Research Center for Women and Families   | 91   |
| Panel Discussion/Questions  | 96   |
| PAPER MILL REPORTING<br>(301) 495-5831  |      |

A F T E R N O O N P R O C E E D I N G S

Afternoon Opening Remarks and Introductions

DR. REPKA: Good morning, soon to be good afternoon. I am Michael Repka, chair of this advisory committee panel, or serving as acting chair. I am a professor of ophthalmology and pediatrics at Johns Hopkins University.

The remainder of the panel are going to introduce themselves. We will start with Dr. Strahlman.

DR. STRAHLMAN: I am Dr. Ellen Strahlman. I am the chief medical officer for GlaxoSmithKline and I am the industry representative on this committee.

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

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

DR. WILSON: M. Roy Wilson, the chancellor at the University of Colorado Denver and professor of ophthalmology.

PAPER MILL REPORTING  
(301) 495-5831

PARTICIPANTS

Michael X. Repka, M.D., Acting Chair  
Yvette Waples, Pharm.D., Designated Federal Official

ADVISORY COMMITTEE MEMBERS (Voting):

Mary A. Majumder, J.D., Ph.D.

ADVISORY COMMITTEE MEMBERS (Non-Voting):

Ellen Strahlman, M.D., M.H.Sc., Industry Representative

ADVISORY COMMITTEE TEMPORARY VOTING MEMBERS:

Natalie Afshari, M.D., FACS  
Warren B. Bilker, Ph.D.  
Paula Cofer, Patient Representative  
William G. Gates, M.D.  
Philip Lavin, Ph.D.  
Marijean M. Miller, M.D.  
Michael X. Repka, M.D.  
M. Roy Wilson, M.D., M.S.

FDA MEMBERS (Non-Voting):

Edward M. Cox, M.D., M.P.H.  
Wiley Chambers, M.D.  
Rhea Lloyd, M.D.

PAPER MILL REPORTING  
(301) 495-5831

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

DR. BILKER: Warren Bilker, professor of biostatistics at the University of Pennsylvania.

DR. AFSHARI: Natalie Afshari, associate professor of ophthalmology at Duke University, Corneal and Refractive Surgery.

MS. COFER: Paula Cofer, FDA patient representative.

DR. LAVIN: Philip Lavin, biostatistics, SGE, with Averion.

DR. LLOYD: Rhea Lloyd, a medical officer with the FDA.

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

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

DR. REPKA: Thank you. This afternoon the committee will discuss the new drug application 22-369, bimatoprost ophthalmic solution 0.03 percent, Allergan, Inc., proposed for the treatment of hypotrichosis of the eyelids.

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

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

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

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

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

PAPER MILL REPORTING  
(301) 495-5831

determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

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

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

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

Today's agenda involves the new drug application NDA 22-369, bimatoprost ophthalmic solution 0.03 percent, sponsored by Allergan Inc., proposed for the treatment of hypotrichosis of the eyelids. This is a particular matters

PAPER MILL REPORTING  
(301) 495-5831

Conflict of Interest Statement

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

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

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

PAPER MILL REPORTING  
(301) 495-5831

meeting during which specific matters related to Allergan's bimatoprost ophthalmic solution 0.03 percent will be discussed.

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

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

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

FDA encourages all other participants to advise

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

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

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

Industry Presentation  
Introduction and Overview

DR. WHITCUP: Good afternoon.

Fist I would like to thank the FDA and the committee for taking the time to review our new drug application of bimatoprost for eyelash growth.

[Slide]

My goal to start off the committee meeting will be to give an introduction and a development overview. I am Scott Whitcup. I head the research and development group. I am an ophthalmologist by training and actually spent about ten years in the Washington area where I was at the NIH.

[Slide]

Following my introduction, Dr. Beddingfield, who ran the clinical program, will review the efficacy data.

PAPER MILL REPORTING  
(301) 495-5831

initial glaucoma studies raised the possibility of an aesthetics use of the medication.

[Slide]

It is not surprising that you might get eyelash growth from an eye drop. On the left side, this is a drop of Lissamine green. It is a stain that is used in clinical ophthalmology. you can see that not only is the eye bathed in medication but also the base of the eyelashes and the skin of the eyelid. So, it is not surprising that we would see eyelash growth.

[Slide]

But the development for eyelash growth was not initiated until we had a fair bit of safety information, and safety was confirmed both in the long-term clinical trials and in extensive postmarketing experience. Today, with this application, we have 32 trials with over 5,700 participants for over 13 years of exposure. Oftentimes when you submit a new drug application you may have 1,000 patient-years of exposure. We have, in this application 8.8 million patient-years of exposure. And, the trials in glaucoma included exposure as much as 40-fold greater than what you will see we are applying now, which is bimatoprost directly to the

PAPER MILL REPORTING  
(301) 495-5831

Then Dr. Sef Kurstjens, who is our chief medical officer, will review the safety data.

[Slide]

This is an aesthetics use. The proposed indication is to increase the prominence of eyelashes or, as the FDA said, to treat hypotrichosis of the eyelids. It was important to us that the clinical effect not only be statistically significant and clinically evident, but important predominantly to the women who participated in the studies and, as an aesthetics use safety was the primary importance in the program.

[Slide]

Bimatoprost, the molecule was first synthesized at Allergan in 1992 as a potential treatment for glaucoma. Clinical trials for the medication in glaucoma started in 1995 and the drug was approved by FDA for glaucoma in 2001 as Lumigan.

Interestingly, eyelash growth was seen in the clinical trials. There is a statistically significant increase in eyelash growth reported in both of the Phase 3 trials. We know that bimatoprost prolongs the anagen growth phase of the hair cycle. So, these findings in these

PAPER MILL REPORTING  
(301) 495-5831

base of the eyelashes, to the eyelid margin.

[Slide]

The drug is very safe for the treatment of glaucoma. The main side effects that we see in patients treated for glaucoma include redness of the conjunctiva, this is due to vasodilation; eyelash growth; itching; irritation and dryness. Inflammation is seen in less than one percent in all of the glaucoma trials. And, iris pigmentation, which is the one side effect that can be permanent, is rare but in the trials it is mostly patients with brown eyes becoming more brown.

But although this is rare, it can be permanent. It is something that we feel needs to be informed to both patients as a possible side effect and to prescribers. As we looked at the glaucoma side effects, we felt that the side effects could even be reduced further by direct application to the base of the eyelashes.

[Slide]

So, as part of the development program we developed an applicator where you are applying five percent of the drop to the base of the eyelashes, so 95 percent decrease in drug exposure, and it allowed us to use the same

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

formulation, the same concentration, the same manufacturing and quality control for the medication.

[Slide]

Here again is exposure with an eye drop again on the skin in the eye. Here you can just see a faint line of dye at the base of the eyelashes. So, much reduced exposure which we felt was appropriate for the aesthetics use.

[Slide]

The question was could we maintain efficacy and improve safety. An open-label trial of bimatoprost directly applied to the eyelid margin was conducted that confirmed both the efficacy and enhanced safety. We then took the glaucoma data, the open-label trial data, went to FDA and the agency then requested a confirmatory randomized clinical trial of bimatoprost applied to the eyelashes.

[Slide]

Three validated instruments that Dr. Beddingfield will go into were developed for the trial. We then conducted the randomized, controlled trial of bimatoprost compared to vehicle. Not only was efficacy maintained, but the major side effect, for example in glaucoma, was conjunctival hyperemia and we were able to decrease this

Safety and following patients does not end with approval and the company is also extremely committed to an enhanced safety assessment post-approval. We plan to do increased frequency of postmarketing review of all reported adverse events in real time; to do aggregate looks at the safety data every three months for three years; signal detection to see if we find anything that we hadn't seen in over ten years of exposure in glaucoma. Given that we have reduced exposure further, we don't expect it but we feel strongly that we must keep up the postmarketing safety at an enhanced rate. In addition, we have developed targeted education emphasizing important safety messaging and information for not only prescribers but also for patients.

Before I turn the podium over to Dr. Beddingfield, I also want to recognize a number of people both from the company and outside experts who helped not only in the program but in preparing for today's committee meeting.

[Slide]

With that, I will turn the podium over to Dr. Beddingfield who will review the efficacy data.

Clinical Overview

DR. BEDDINGFIELD: Good afternoon. I would like to

from 45 percent to 3.6 percent and, in fact, in the eyelash growth trial this was the only adverse event that was statistically significantly greater than patients receiving vehicle.

[Slide]

In the end, approval decisions are about benefit and risk. The benefit is that we do see increased prominence of the eyelashes. This benefit and this growth of eyelashes is highly statistically significant and clinically evident. But, again, the important piece was that in all of the patient reported outcomes the participants, predominantly women in these studies although we did have some men in the pivotal trial, showed that it was important to patients. Dr. Beddingfield will go over the patient reported outcomes as well.

But, again, as an aesthetics product, safety is of prime importance and we are fortunate to have long-term safety data, again, with 32 trials, 8.8 million patient-years of exposure, and we were able to enhance that safety further with direct application with sterile applicators to the eyelid margin.

[Slide]

thank the committee for reviewing our briefing package and spending your valuable time here today, and I would like to thank the FDA for convening this meeting.

[Slide]

My name is Frederick Beddingfield. I am the head of dermatology clinical research and development at Allergan. I was the clinical lead for the bimatoprost eyelash growth program, and I am a dermatologist, also on the faculty at UCLA where I teach and see patients.

[Slide]

Today I am going tell you about the clinical development program, with a focus on the efficacy. The efficacy really began, as Dr. Whitcup said, with the two Phase 3 trials in glaucoma which documented eyelash growth.

With the wealth of safety data that we then collected in the post-approval period, we started considering an aesthetic indication for eyelash growth and developed a new method of application with which we could decrease the amount of drug applied dramatically and then apply it to the eyelid margin.

We then confirmed this in an open-label trial where efficacy and safety were superb. Following this, we

ProTEXT Transcript Condensing for Windows

initiated discussions with the FDA. We validated and developed three scales and then, on the request of the FDA, we performed a pivotal trial with bimatoprost applied to the eyelashes.

[Slide]

Just to review the glaucoma Phase 3 trials, studies 008 and 009 were the pivotal trials. These were identical trials. There were three arms. There was a Lumigan QD arm, a Lumigan BID arm and a timolol active control arm. As you can see from the slide, the timolol group effectively had no eyelash growth, whereas the Lumigan QD and BID groups showed substantial eyelash growth. In fact, at all time points in both studies at three, six and 12 months these differences were significantly different in terms of the eyelash growth versus timolol.

[Slide]

You may be wondering why does a drug that was initially developed for lowering IOP actually increase eyelash growth. Hair, regardless of where it is, it has three cycles. It has an anagen phase, which is a growth phase; a catagen or transitional phase and then a telogen arresting phase. In the eyelashes in particular, these

conducted, and this was conducted by an investigator who was an ophthalmologist.

Twenty-eight female subjects were involved. They applied the product to the eyelid margins daily for three months. Safety and efficacy were evaluated and, because he was an ophthalmologist he did a complete ophthalmologic examination including ophthalmoscopy, biomicroscopy, visual acuity and IOP.

The results showed that at month three 100 percent of the patients in the trial had experienced eyelash growth.

In terms of safety, in fact, we do prove the concept that you could actually improve the tolerability of what was already a well tolerated drug, and there were no adverse events that led to discontinuations. There were no serious adverse events and there were no adverse events related to visual acuity or vision. In fact, the adverse events that were seen were mild and transient and IOP showed no statistically significant change from the baseline values.

[Slide]

At this point, and with discussions with the FDA and with the indication that we would need one additional trial, applying in this manner to the eyelid margin for

phases are fairly short.

The anagen phase is about one to two months and the telogen phase is about four months. What bimatoprost does is it actually increases the length of that anagen phase, and it also increases the proportion of hairs that are in the anagen phase by converting telogen hairs into anagen hairs. Because of that, because you are growing for a longer period and you are in this longer phase of growth, you get longer and thicker eyelashes.

[Slide]

I will talk about the clinical development program overall and then I will tell you about the three efficacy scales which we spent a lot of time developing, and we knew that these scales were quite important because this is an aesthetic use and we wanted to be able to show not only that eyelashes grew but that it was important to the patients, and that is why the patient reported outcomes were very important. Then I will discuss the results.

[Slide]

Again, once we developed this methodology for applying only five percent of the usual drop applied for glaucoma to the eyelid margin, an open-label trial was

eyelash growth, we designed the scales and we designed a Phase 3 confirmatory trial for bimatoprost for eyelash growth.

This was a multicenter trial. It was randomized, double-masked, vehicle-controlled. Sixteen sites participated in the trial and subjects were randomized in a 1:1 fashion to bimatoprost versus vehicle. The subjects were treated daily in this manner for four months and then there was a one-month follow-up period.

The primary endpoint, as was agreed to a priori with the FDA, was the Global Eyelash Assessment scale, which I will go into in detail in just a moment. It was a responder definition. On this four-point scale subjects had to improve by one grade in order to be a responder, and then we compared the bimatoprost and vehicle rate at week 16.

Secondary endpoints were more quantifiable digital or photographic image analyses of the individual components of overall eyelash prominence. That was the length, the thickness and the darkness of the lashes. So, we tested those by photographic assessments.

Finally, the patient reported outcomes were other endpoints that were observed. We had 23 questions in three

ProTEXT Transcript Condensing for Windows

domains, and I will go into those in more detail as well.

Of course, as Dr. Whitcup mentioned, safety was of concern. At some sites the investigators were not ophthalmologists so we had an ophthalmologist involved at every site to assure that we could do ophthalmoscopy, biomicroscopy, IOP and visual acuity at all sites at all visits. So, those examinations were performed in addition to routine adverse event monitoring.

[Slide]

This just shows how this method of application is and how it is different from applying a drop to the eyelid for glaucoma. So, a drop is applied to an applicator and then it is simply swiped across the base of the eyelashes at the eyelid margin. The benefit of this is that we have reduced the drop by 95 percent so we are applying only 5 percent, and now we are not applying it to the eye; we are actually applying it directly to the skin where it needs to be to stimulate eyelash growth and where there is also a skin barrier to reduce exposure further.

[Slide]

I would like to now switch gears and talk to you a little bit about the three efficacy measures that we used.

PAPER MILL REPORTING  
(301) 495-5831

[Slide]

I will talk a little bit now about the Global Eyelash Assessment scale. Again, it is a live, face to face assessment. In the clinic the doctor looks at the patient's lashes and rates them on overall eyelash prominence based on length, thickness and darkness, but with an emphasis on length. It is a four-point ordinal scale.

It is an aesthetic assessment. What I mean by that is that when the doctor looks at the patient they just evaluate them in the office. It doesn't matter where they were on the last visit. It doesn't matter where they will be in the next visit. They just rate them today, where are you on this four-point scale.

[Slide]

We realized that to aid in the doctor's evaluation we needed to create a photo guide with representative photos from the four different points on the scale. Those four points on the scale were eyelash prominence rated as minimal, moderate, marked or very marked. So, we started with 400 photos in order to create this photo guide. We had five physicians' assessment and we did a consistency assessment, and we looked at which photos were most

PAPER MILL REPORTING  
(301) 495-5831

The first was a physician Global Eyelash Assessment scale. So, we wanted a live assessment, face to face. The physician and the patient were in the office. The doctor looks at the eyelashes and rates them globally on overall eyelash prominence. We developed the use of a photo guide so that when they are actually looking at a patient in front of them they can rate them on the four-point scale. So, that was the primary efficacy endpoint.

Then we developed these digital image analyses to look at the three components of overall eyelash prominence, length, thickness and darkness. Why those three components?

That really came from the early work we did with patient focus groups, finding out what is it about eyelash prominence that is important to you. What they told us was that it is length, and that is the primarily important thing; thickness and darkness.

Finally, the patient reported outcomes, and what we were really attempting to do here was to really triangulate with these three measures on a benefit that could not only be shown by objective measurements, but could also be seen as clinically important to the patient because it is an aesthetic indication.

PAPER MILL REPORTING  
(301) 495-5831

consistently assessed as falling into one of these four categories.

We were then able to wean that number down to 64 photos and we presented these to another ten physicians who also assessed these 64, and they were able to put 16 in each grade. From this, we finally came up with our photo guide which has three subjects per grade. So, we have 12 subjects total in the photo guide. This is actually in your briefing book. If you want to look at that, it shows you representative photos.

What we really found from this photo guide and what you will see from the next picture is that patients and doctors actually, if you ask them can you rate someone's eyelashes with this photo guide, looking at this, actually tell you they can do it pretty readily.

[Slide]

So, here is a representative photo from the photo guide, patients with minimal, moderate, marked or very marked. But, of course, we wanted more than just anecdotal evidence that doctors could do this reliably so we did another study to look at the inter- and inter-rater reliability.

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

[Slide]

This was study 003. It was a single-center study and 68 subjects participated, with seven physicians. What we did was, in order to analyze the inter- and intra-rater reliability, we had 68 subjects come through in our randomized order. They saw seven physicians who are randomized in the order in which they were seen. We waited at least an hour and then the 68 subjects were re-randomized. They went through and saw the physicians in a re-randomized order.

By doing this, we were able to say amongst these seven physicians if they evaluate the same patient twice, do they evaluate them the same. So, the inter-rater reliability and the intra-rater reliability, when the same physician saw the patient twice, did they rate them the same both times?

In addition, in this trial we used this opportunity to work on patient reported outcomes further and to further refine our digital image photography.

[Slide]

The results were really astounding. There was almost perfect inter-rater reliability, with a Kendall

Then the patients reported outcomes measure, of course, are how this all affects the patient and what it means to them. It is very important. It is an aesthetic indication. So, we worked with John Ware who created the SF-36, an external expert, on developing these health outcomes measures. We started this actually early on with patient photo focus groups. We tested these in the early open-label trial, and in the 033 study we further refined these, and with further patient groups we narrowed it down to 23 questions on satisfaction.

These fell into three domains. The first domain was how is your satisfaction related to eyelashes in terms of their physical attributes, primarily the length, thickness and darkness? And subjective attributes, how does this make you feel about yourself, your attractiveness, your confidence, and items such as that? Then, finally, how do these eyelashes affect your daily routine?

[Slide]

I would like to now switch gears and talk about the results. I am very happy, actually, to be able to talk to you about the results today because, of all the studies I have been involved in, this is the only one where we

statistic of 0.855, and substantial intra-rater reliability, with a weighted Kappa statistic of 0.77. So, we were quite pleased with these results.

[Slide]

Then we went to the digital image analysis. To create these, we worked with external experts. We worked with Kenfield who has participated in many registration trials where photographs were necessary in the ophthalmologic and dermatologic realm. They helped us develop measurements for length, thickness and darkness.

We had to make sure that the photos were taken in a way so that they would be uniform. So, they created what I refer to as a stereotactic instrument where the patient puts their head in this device. It is held a certain distance from the camera which has very uniform settings. Measurements are taken to make sure that the analysis will be correct. Then the photos, once taken, are actually uploaded immediately and they are evaluated to see are these photos that we can actually do these analyses on. If they are not, the photos are retaken in real time. We used this, again, to look at length, thickness and darkness.

[Slide]

actually hit every single endpoint that we looked at and the results were really astounding.

[Slide]

In terms of demographic data, there were 137 bimatoprost patients, 141 vehicle patients. There six early terminations in the bimatoprost group and 15 in the vehicle group. There were four early terminations due to adverse events in both groups.

To enroll in this study on that four-point scale you had to be a minimal or moderate, a 1 or a 2. Twenty percent of the patients were in the minimal category and 80 percent were in the moderate category. These groups were evenly distributed against the bimatoprost and the vehicle group.

[Slide]

In terms of age characteristics, the average age of the patient in the study was 50. About a third of the patients were under 45; about 60 percent were in the 45-65 category; and roughly 8-10 percent were in the over 65 category. The range of ages was 22 to 78.

In terms of gender, as you might imagine, most of the subjects were female, 97 percent. In terms of race, we

ProTEXT Transcript Condensing for Windows

had 20 percent of the subjects in our study that were non-Caucasian patients, skin of color, and the majority of those were Asian and Hispanic.

[Slide]

This is the primary efficacy endpoint which, again, is the Global Eyelash Assessment scale at week 16. It is a responder definition. You had to improve at least one grade on that four-point scale in order to be a responder.

What you see here is actually that at week one you see starting to show a difference between the blue group, which is the percentage of responders in the bimatoprost group, and the yellow group, which is the vehicle group. This is statistically significant when half the subjects are responders at week eight. At the primary endpoint, week 16, 78 percent of the subjects in the treatment group versus 18 percent of the subjects in the vehicle group are responders.

This effect is maintained throughout the four-week follow-up period.

[Slide]

To check the robustness of the primary endpoint, we split these patients into two sub-studies and did 1,000

Assessment in that there is an early separation between the treatment group and the vehicle group. This is a measurement of eyelash length over time. What you see is that at week 16 eyelash length has actually increased by 25 percent in the treatment group versus two percent in the vehicle group. This is the patient who represents the closest to the mean change in the entire study in the bimatoprost-treated group. So, you can see what the average change really looked like in length.

[Slide]

Now switching to thickness, you can see almost an identical curve, again statistically significant here by week eight, maintaining throughout the treatment period and into the post-treatment follow-up period. These patients actually increased their thickness by 106 percent in the treatment group versus 12 percent in the vehicle group.

[Slide]

In terms of eyelash darkness, a very similar curve here. At week 16, an 18 percent increase on average in darkness of eyelashes in the treatment group versus three percent in the vehicle group. This is the patient who best represented the average increase in eyelash darkness at week

simulations, and the maximum p value in these simulations was p equal to 0.000000228.

This is a representative photograph of a subject who was a 2, or moderate, at baseline and was marked, or 3, at week 16.

[Slide]

Now, at the request of the FDA we actually looked at a two-grade increase on this four-point scale and this is, of course, a more rigorous way of looking at this and a more difficult endpoint to achieve. That is evident from the fact that there is essentially no placebo rate. However, even with this more rigorous assessment, one-third of the subjects at week 16 are responders.

Here is a representative photo of a subject who was a Global Eyelash Assessment score of 2 or moderate at baseline and achieved very marked, or a score of 4, at week 16.

[Slide]

In terms of those photographic digital image analyses of length, thickness and darkness, I will go over those now. What you find is that the results look very similar to the results I showed you for Global Eyelash

16 in the bimatoprost group.

[Slide]

We looked at the patient reported outcomes. Again, you will remember that there were 23 questions. All were statistically significant at week 16. In particular, I would like to call your attention to the overall satisfaction with eyelashes, item 4, which was statistically significant at a high level. Then, the individual components, the domains 1, 2 and 3, physical attributes, subjective attributes and daily routine, were all highly statistically significant at week 16.

[Slide]

Now, one of the things that was important to us was to say, okay, we have been able to document that patients are satisfied. How did these measures relate to each other? As you remember, we were trying to triangulate in on this benefit.

So, we looked at the concordance of these efficacy measures and I would like to just show you this graph. This is the number of changes in Global Eyelash Assessment at week 16. So, let's say a patient changed by one grade so they would have been counted as a responder on the primary

analysis, how did they do on those other assessments? So, on average this group that changed one grade on Global Eyelash Assessment score increased length by 1.3 mm. Overall, that group, 65 percent of them, were satisfied.

Now, if you look at that stringent hurdle of two grades, this group increased their eyelashes by 2.1 mm and 91 percent of them were satisfied. Then you might say, well, what about those people who were non-responders, this group who had zero grade changes? You actually notice that almost a third of them were satisfied.

Why is that? That is because Global Eyelash Assessment is overall prominence. That is what we are assessing. But these people actually, by and large, still responded on some of the individual components, and you can see that they did have an increase in eyelash length, and they did have an increase in satisfaction.

If you look at all the patients in the bimatoprost group, of the 137 subjects, only two didn't respond either on the Global Eyelash Assessment or the digital image analysis.

[Slide]

So, in summary, all the primary and secondary

PAPER MILL REPORTING  
(301) 495-5831

[Slide]

But first, it is very important to appreciate that bimatoprost for eyelash growth and for glaucoma involved exactly the same medication. So, it is the same formulation; it is the same concentration; and both are applied topically, for glaucoma directly into the eye involving eyelid exposure and in the eyelash growth trial it is applied to the lid margin. As has already been mentioned, it delivers only five percent of the volume of the drop administered for glaucoma.

[Slide]

The safety for bimatoprost has actually been very well established, and I will be sharing that with you. We have a very large safety database from clinical trials. We have over 5,700 patients participating in 32 studies that have spanned 13 years. This includes six long-term trials of greater than one year's duration and it includes once daily dosing as well as twice daily dosing.

The adverse events from those trials are predictable. They are dose-related and, with one exception, which is iris hyperpigmentation, they are reversible. We also have postmarketing experience. It has been available

PAPER MILL REPORTING  
(301) 495-5831

endpoints were met. They were met to high statistically significant degrees, including the patient reported outcomes which we knew were very important in this indication. We also showed concordance across the three measures. These results were also consistent across age and race groups in the study.

[Slide]

Thank you very much. At this time I would like to turn the podium over to Dr. Sef Kurstjens who will discuss the safety.

#### Safety Overview

DR. KURSTJENS: Good afternoon. My name is Sef Kurstjens. I am the chief medical officer at Allergan. Included in my responsibilities is oversight of the safety of Allergan's products.

As Dr. Whitcup has already mentioned, safety was a key consideration for us when it came to initiating this new aesthetic indication for bimatoprost. What I will be doing in my presentation is providing an overview of the extensive safety experience that we do have with bimatoprost and glaucoma indication, and using this to put the safety experience into context.

PAPER MILL REPORTING  
(301) 495-5831

commercially for seven years now, with about 8.8 million patient-years of exposure, and we see no new safety signals.

[Slide]

What is represented on this chart is the substantial safety database experience. As you can see here, we have the 32 clinical trials represented, first approved by the FDA in 2001, with seven years experience, and approved now in over 80 countries and involving 8.8 million patient-years of exposure.

What I will be doing is providing you some degree of characterization of the adverse events from the clinical trials and I will be drawing on these six long-term studies.

So, they include the two pivotal trials from the original glaucoma indication which ran for a year, also the four-year extension, as well as three additional one-year trials. These trials involve in total 1,400 patients exposed to bimatoprost 0.03 percent either once or twice daily.

[Slide]

So, what is presented here is the duration of exposure for most studies. You can see that we had about 1,200 patients treated for six months, 600 for a year and over 150 for two years. So, it is substantial exposure.

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

[Slide]

Looking now at the demographics from these trials, the average age was around 61 years of age, with about 50 percent of patients in the 45-60 year-old age group. Importantly, we had somewhere on the order of about 140 patients less than 45 years of age. There was similar distribution between males and females, and very representative distribution across all races. It actually very closely mirrors the U.S. population.

[Slide]

So, looking at the adverse events that were most frequently reported in the studies out to 12 months, you can see them represented here. They are conjunctival hyperemia, growth of eyelashes, which has obviously led us to investigate this further in the new aesthetic indication, eye pruritus or itchiness, eye irritation, dry eye and skin hyperpigmentation and, rather unsurprisingly, the incidence of these adverse events are a little higher in the BID than in the once daily dose group.

[Slide]

So, characterizing these adverse events a bit more in terms of demographics, what you can see represented here

PAPER MILL REPORTING  
(301) 495-5831

reported within the eyelash growth trial and comparing it to that seen in the glaucoma study after four months. Again, to orient you, the amount of bimatoprost applied in glaucoma was around 20 times greater than the eyelash growth indication for the once daily group compared to 40 times greater compared to the eyelash growth in the BID group.

Rather unsurprisingly, you see a dose-response relationship so if you look at conjunctival hyperemia, the most frequently reported adverse event, it was around 52 percent in the BID group and around 39 percent in the once daily, and greatly reduced, to around 3.6 percent, in the eyelash growth trial.

In fact, if you do an unadjusted, sort of very conservative statistical comparison between active and vehicle in the eyelash growth study there is only one adverse event that ends up being statistically significantly different, and that is conjunctival hyperemia.

[Slide]

Moving now to discontinuations due to adverse events, again as one might expect because of the difference in dosing, the adverse event discontinuation rate was somewhat higher in the BID group, around 11 percent; around

PAPER MILL REPORTING  
(301) 495-5831

are the adverse events reported by Caucasians and Blacks and, again, the incidence of adverse events is very similar between race groups. Importantly, skin hyperpigmentation was very similar and, as Dr. Beddingfield already mentioned, the growth of eyelashes, again, was similar between Caucasians and Blacks.

[Slide]

Looking now at the effect of age and the incidence of reporting of adverse events, again there was very similar reporting of adverse events across these three age groups, perhaps with the exception of conjunctival hyperemia which is a little higher in the younger age group.

[Slide]

What this slide does is give an idea of the onset of adverse events by contrasting the incidence of adverse events at four months with 12 months, and you can see, in fact, a very similar incidence of reporting between month four and month 12, indicating that if the patient were to experience an adverse event they were most likely to do so within the first four months of treatment.

[Slide]

Let's move now to looking at the adverse events

PAPER MILL REPORTING  
(301) 495-5831

6 percent in the once daily group; and greatly reduced, to around 2.9 percent in the active from the eyelash growth trial and very similar, in fact virtually identical to vehicle.

For the glaucoma subjects the most frequently reported adverse event ended up being the adverse event most commonly associated with discontinuation but, again, the discontinuation rate was very low in the once daily group, about 3 percent.

[Slide]

So, looking at the adverse events that led to discontinuation in the eyelash growth trial, there were actually four in each treatment group. In terms of patients treated with bimatoprost, there were two-treatment related discontinuations due to dermatitis; one treatment-related discontinuation due to dry eye; one non-treatment related discontinuation due to eye inflammation.

Similarly, four in vehicle, one treatment-related discontinuation due to low IOP, remembering that this was obviously a masked trial; one treatment-related discontinuation due to eyelid erythema; two non-treatment related discontinuations for lymphoma; and conjunctival

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

hemorrhage.

[Slide]

What we have done as well is to look at rare adverse events that might be of interest for Lumigan, and for that we have referenced the USPI. The adverse events that are considered to be rare but of importance include iris hyperpigmentation, macular edema, eye inflammation and iritis. These events are reversible with discontinuation of treatment, as we have said before, with the exception of iris pigmentation.

So, when we looked at the bimatoprost group in the eyelash growth study there was one report of iris pigmentation, which was actually very questionable because it was reported to have resolved by the end of the study while the patient was still on treatment. There was one report of eye inflammation that was, indeed, preexisting.

[Slide]

In terms of serious adverse events, there were three serious adverse events reported from the eyelash growth trial and none of them were treatment-related. Two subjects in vehicle had serious adverse events of lymphoma and of recurrent metastatic breast cancer. One subject in

PAPER MILL REPORTING  
(301) 495-5831

[Slide]

What is provided here is an analysis for the entire population and at the lower end of the chart looking at patient outliers. So, starting with the entire patient population first, the mean IOP at baseline for both treatment groups was around 14.5 mmHg. By week 16, this was 13.9 in the vehicle and 13.3 in the active treatment group.

There were some small statistically significant between group differences at some of the visits during the study but all of them are less than 1 mmHg and weren't considered to be clinically relevant.

So, to put that into context here is what you do, you take an average of each of the individual subject's maximal excursion in intraocular pressure across the study.

That value comes to 3.7 for vehicle and 3.9 for BEG. So, not only are those two values very similar, but it helps put in context this 1 mmHg falling within normal variations seen in changes of IOP.

Looking now at the number of subjects whose lowest IOP was less than 10 mmHg, there were 18 in the active treatment group from the eyelash growth trial and 16 in vehicle. Those distributions are very similar. In fact,

PAPER MILL REPORTING  
(301) 495-5831

BEG had a non-treatment related serious adverse event of squamous cell carcinoma of the skin on the back.

[Slide]

So, what are the advantages of Lumigan being available for sometime commercially now is that there has been quite a lot of investigation looking at the pharmacology of this drug and associating it with some of the adverse events that were seen so we can actually understand what is driving a lot of the adverse events.

So, we understand that conjunctival hyperemia is associated with vasodilation. We understand that eyelash growth, as Dr. Beddingfield already mentioned, is associated with prolonging the anagen phase of the growth cycle within the hair follicle, as well as having transition from telogen back to anagen. Importantly, hyperpigmentation has been very well studied in both the skin and the iris, and it has been noted to be due to an increase in melanin with no cell proliferation or atypia.

Obviously, the pharmacological effect associated with bimatoprost is its effect on reducing intraocular pressure and, hence, its approval in glaucoma, and so this is very well characterized in our eyelash growth trial.

PAPER MILL REPORTING  
(301) 495-5831

when you test them statistically there is no difference. Focusing on what might be an IOP of interest, less than 5 mmHg, there was only one occurrence and that was on vehicle.

[Slide]

Obviously, the other advantage with Lumigan is that we have extensive postmarketing experience with this product. It has been available since 2001. More than 65 million bottles have been distributed, equating to about 8.8 million patient-years or exposure. We have had actually an extremely low reporting rate associated with this on the market, with only about 6 events reported per 10,000 patient-years of exposure and the adverse events that have been reported are, in fact, those which are already described within the Lumigan label. So, we see no new safety signals.

[Slide]

In summary then, the safety of bimatoprost has been well established in glaucoma and is relevant for the eyelash growth indication. We have a very large safety database from clinical trials, over 5,700 participants, 32 trials, 13 years, very substantial. It includes six long-term studies of greater than a year's duration, both once

PAPER MILL REPORTING  
(301) 495-5831

daily and twice daily dosing.

The adverse events are mild and predictable in terms of timing and in terms of their pharmacology. They are dose-related and, with the exception of iris hyperpigmentation, they are reversible.

We see no new safety signals from our extensive postmarketing experience. In terms of the eyelash growth indication, it is important to note that bimatoprost for eyelash growth and glaucoma involved the same formulation and the same concentration, and by applying it to the lid margin it actually reduced by 95 percent the volume administered. As a result from that, we see adverse events which are similar in profile but, obviously, at a much, much lower incidence.

[Slide]

Let's move now to what our plans are in terms of risk management. Obviously, risk minimization is one of our important considerations and a key part of that is communication, communication to both physicians as well as patients through the labeling.

We think it is very important to manage against the risk of infection by providing sterile single-use

PAPER MILL REPORTING  
(301) 495-5831

So, in conclusion, Dr. Beddingfield has shown you that bimatoprost has been shown to improve eyelash prominence. This being an aesthetic indication, safety is obviously critical. We have extensive long-term safety with the topical application to the eye. The adverse events are well characterized. They are predictable.

We substantially decreased the drug exposure with sterile application to the base of the eyelashes, improving the tolerability considerably. Nevertheless, we do remain committed to making sure that we have great vigilance in the approval process and throughout commercialization.

That concludes the presentation and, on behalf of Allergan, thank you for your attention.

Questions/Clarifications

DR. REPKA: Thank you for your presentation. I would like to open the floor to the panel for questions to the presenters. Dr. Majumder?

DR. MAJUMDER: Yes, I wondered if you had any data on the duration of the effect after discontinuation of treatment, and kind of the point of the question is I am wondering if this is something patients would use intermittently, using it and then stopping it at

PAPER MILL REPORTING  
(301) 495-5831

applicators which will be packaged with the solution. The solution itself is sterile and formulated with a preservative.

We can't over-communicate so we are planning on targeted education, emphasizing key safety messages to both patients and prescribers. Allergan being an established pharmaceutical company, we have a very robust pharmacovigilance system where we are able to evaluate both single adverse event cases as they are reported to us, as well as perform aggregated analysis with data mining, looking for signals not just from spontaneous reports but also from all sources of data.

What we intend to do going forward is to make sure that we are able to distinguish between the two different indications for bimatoprost. So, by providing a targeted questionnaire we will be able to get more information about the route, the use and the demographics.

We are also doing, as Dr. Whitcup mentioned, significant periodic reviews every three months for the first three years and we are happy to share that information with the agency as required.

[Slide]

PAPER MILL REPORTING  
(301) 495-5831

prespecified intervals, or are they going to be using it continuously for the rest of their lives. Any data that bears on that issue?

DR. WHITCUP: Thank you for the question. I will have maybe Dr. Beddingfield comment as well, as needed. From the glaucoma literature we have a fair bit of information that as the hair cycle takes about four to six months to go through, if patients stop using the medication they will go back to baseline in that period of time.

So, there are no adverse effects of stopping. It is not like your lashes end up worse, but if you want to maintain the effect you need to continue the medication. Which is, again, why we waited a fair bit of time to have 13 years of patient experience before we came forward to the agency for the aesthetics use.

DR. REPKA: Dr. Afshari?

DR. AFSHARI: I was wondering if there are any studies about prolonging the anagen phase of the hair growth on another part of the body, such as the hair on the head, and are there any side effects from that or any problems within the hair follicle, such as tumor growth over time or anything like that. Are we sort of stopping mitosis in the

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

GI phase of the cell cycle, or what are we doing exactly to the follicle?

DR. WHITCUP: In addition to the clinical data, we have a wealth of preclinical data in animal studies as well and we haven't seen adverse effects on the hair follicle. There has been interest in, you know, could this be used elsewhere, such as the scalp, given the low amount of volume and that it is not formulated to get in through the scalp. We don't have data on that. Maybe Dr. Beddingfield can comment on use outside of the eyelashes.

DR. AFSHARI: Is there any other medicine that would prolong the hair cycle such as this of another class?

DR. BEDDINGFIELD: Our understanding is that minoxidil also prolongs the anagen phase of scalp hair when it is used in that way. Although the exact mechanism by which it does that is not clearly understood, we do understand that it has a similar effect. As Dr. Whitcup mentioned, from the wealth of preclinical data we have, you are really extending that anagen phase. You are not actually changing the cells in terms of producing atypia or tumor. There is no suggestion of any of that. Thank you.

DR. REPKA: Thank you. Dr. Bilker?

PAPER MILL REPORTING  
(301) 495-5831

eyes they may become brown-pigmented with continued use. We also know that if you stopped medication then that change stopped but, as has been noted, may not regress and go back.

DR. BILKER: Were they all in whites or Caucasians? Any in Blacks?

DR. WHITCUP: There weren't. It seemed to be related to iris color, less to race.

DR. REPKA: Dr. Wilson?

DR. WILSON: On the efficacy study, if I remember right, there were about 16 centers and about 270 patients. Any explanation for why there was only one Black? Do they have less hypotrichosis or something?

DR. BEDDINGFIELD: Thank you for the question, Dr. Wilson. That was certainly something that we looked at. We did have 20 percent of the patients who were non-Caucasian.

Amongst those only one of the subjects was African American and they were randomized to vehicle.

One of the reasons is that with the digital image analysis, which was a critical part of the study, it turns out that if you don't have quite as much contrast between the lash, which is the signal, and the background skin which, in this analysis, was considered the noise, then it

PAPER MILL REPORTING  
(301) 495-5831

DR. BILKER: I have a question about iris pigmentation. I know those numbers are small, but in brown eyes, for instance, you had said that it was mostly darker pigmentation. What are the effects in other eye colors, and were there any race differences in those that had that adverse event?

DR. WHITCUP: Thank you, Dr. Bilker. In our trials--and these are coming from the glaucoma trials because with less drug exposure we may never see changes in iris pigmentation with this use although we want to be very conservative in warningsB-it was mostly brown eyes where, if you followed specifically with photos, the irises looked a bit more brown. We have never seen in our studies with bimatoprost blue eyes, that I am aware of going to brown. Sometimes they may be sort of a grey-brown, noted to have a bit more brown pigment.

In most of the studies the patients have not noticed it. There are rare reports in the literature where you do see a more noticeable color change. In our initial Phase 3 trials I believe all of the patients were just brown that looked like they were becoming more brown. But I think we need to tell patients that if they have lighter colored

PAPER MILL REPORTING  
(301) 495-5831

is harder to get acceptable baseline photographs. So, several African Americans, it turned out, did not meet the criteria for screening of the original photographs and, therefore, did not enroll in the trial.

Having said that, the wealth of data that we have from glaucoma studies in which there were approximately 18 percent African Americans exposed to 20-40 times dose suggest that this is safe, and they do experience similar amounts of eyelash growth, as well as similar amounts of adverse events, and it is equally well tolerated.

DR. REPKA: Dr. Afshari?

DR. AFSHARI: The patients who had conjunctivitis and what you called conjunctival hyperemia, was it throughout the use of medicine or did tolerance build after some time, a couple of months into the medicine?

DR. WHITCUP: Thank you, Dr. Afshari. Again, this is not a harmful event; the vessels dilate. In the glaucoma trials in many patients after the first week or two the hyperemia actually goes away. For those who stopped the medication, usually within a week to two, it would resolve if it doesn't go away on drug. In the eyelash growth study we were applying less directly to the eyelid and the rates

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

were very low, about just over three percent. There, where hyperemia has occurred, and in the pilot study as well, it resolves within a week or so. So, very quickly if the drug is stopped.

DR. AFSHARI: One more question, and that is among the rare adverse events there was one patient with eye inflammation. Was it iritis or was it just hyperemia?

DR. WHITCUP: As the uveitis guy, you know, I took interest in that case. It was actually a patient who had undergone previous surgery and prior to entering the study had an epiretinal membrane. So, on one of the visits it was noted that it was that epiretinal membrane with potential inflammation. So, as a cautionary matter, that was noted.

But the patient had 20/20 vision. The patient was, to be cautious, taken off the medication and it stayed the same. So, as best we can tell, the patient came into the study with what was noted as inflammation. It was basically an epiretinal membrane post cataract surgery, but not felt to be related potentially to the drug.

DR. AFSHARI: Thank you.

DR. REPKA: Dr. Miller?

DR. MILLER: I don't remember, in your study did

you exclude patients that had preexisting nevi of the lid or any pigimentary lesions?

DR. WHITCUP: No, that was not exclusionary criteria.

DR. MILLER: I am just wondering if you have any experience through the glaucoma data of patients that did have pigimentary lesions of the lid, if there was any darkening or change, or any experience with problems with that. If that might, in fact, be something you would have to put in labeling or such.

DR. WHITCUP: That is, you know, a very important point. In our postmarketing surveillance we have not seen that in the glaucoma studies specifically. It wasn't noted as an adverse event. So, we haven't seen it reported. It is something that we continue to follow.

There was a focus initially, as I think Dr. Chambers can comment, when this class of medications was first approved to look very closely at pigmented lesions and development of new pigmented lesions, and that hasn't been seen.

DR. MILLER: But it sounds like you have decided the mechanism is increased melanocyte size and not other

atypia, and such. So, that is a little reassuring.

I have an additional question, if that is all right. Do you have any examples of the applicator here? The reason I ask that is that we are approving a medication with a specific type of applicator, and I work with kids and things happen, like the applicator sticks the lid. Did you have any problems with people having trouble using the applicator, causing harm to the eye?

DR. WHITCUP: That is also an important question. We spent a fair bit of time looking at the design of the applicator, focusing on two things, one, making sure that it is not sharp and, two, making sure that it was sterile. You know, we view this actually as an opportunity to provide good patient education on proper use of aesthetics products around the eye.

The FDA actually recently came out with guidelines on how to safely apply some of those, everything from clearly making sure you apply them in as clean a method. Over-the-counter products don't have sterile applicators so this will be a benefit. But Dr. Beddingfield can comment as well that patients in the study did not have trouble applying this. This was something that came natural to

them. We have no reports of injury, and spent a lot of time making sure that these aren't sharp, and no different than other applicators.

DR. MILLER: Is there sort of a flexible tip? It is not like a pencil tip?

DR. WHITCUP: Correct.

DR. REPKA: Dr. Lavin?

DR. LAVIN: A question that I have in your long-term registry in your glaucoma patients, what percentage of them would you estimate become very marked and become marked? Just so I get a sense for the long-term exposure and what eventually happens to these people at steady state in terms of the GEA score.

DR. WHITCUP: This is in the glaucoma trials?

DR. LAVIN: Yes.

DR. WHITCUP: So, in the glaucoma trials we didn't really do those assessments. We mostly know, just from looking at photographs that we have taken for iris color, that probably you get about a grade of 3. It is rare that the eyelashes grow to become a problem. That is a question that often comes up. So, it usually plateaus in about the 3 range for most patients. I think, as Dr. Beddingfield said,

it sort of depends on where you start. So, if you start with sort of a grade of 0 or 1, the predominance you gain may be two grades, one to two grades.

DR. BEDDINGFIELD: Just one other point on that, we did do an analysis in the BEG trial of where people started.

Of the 20 percent of subjects who were minimal at baseline, 100 percent of those increased by at least one grade versus approximately 78 percent in 80 percent of subjects who were grade 2 at the start. With the duration of anagen being one to two months in the normal eyelash, we don't expect eyelashes to grow too long. It is a fairly rare occurrence in glaucoma.

DR. LAVIN: Are there any prognostic factors as to what makes a patient not become a grade 3 or a grade 4? Have you looked at that yet?

DR. BEDDINGFIELD: Well, indeed, if you look at the data that we have, only roughly 20 percent of the subjects did not become a grade 3 or a grade 4 based on the scoring that was used. Most of those subjects do increase on the individual parameters of length, thickness or darkness. Across all of those, the only prognostic factor is that people who start at a minimal level are more likely to

PAPER MILL REPORTING  
(301) 495-5831

to talk about that question. They did extensive analyses on the digital image analysis and the coefficient of variability data.

DR. CANFIELD: We had skin imaging studies. We designed the imaging method and also performed the analysis on all the images. As far as the testing that went into it, we did extensive pre-study testing to validate the method. We had technicians perform test/retest within day, over several days, and then looked at the statistics that came from that. I don't have it in front of me, but from memory, the 95 percent confidence interval, all the statistics for correlation were 0.9 or better.

DR. REPKA: Thank you. Dr. Gates?

DR. GATES: Was age a determinant as far as effect? In other words, do older patients do better or do younger patients do better? Was that looked at?

DR. BEDDINGFIELD: The differences between age were not statistically different on the primary endpoint, but the absolute responder rate is slightly higher in the over 65 population. Again, I think that is because that is somewhat correlated with starting with minimal and 100 percent of the minimal subjects were responders.

PAPER MILL REPORTING  
(301) 495-5831

achieve a one-grade response, and starting at a minimal level is slightly associated with older age. So, older age subjects being more likely to be minimal, are more likely to slightly increase by one grade or more.

DR. REPKA: Let me ask a follow-up question after Dr. Lavin. What is the test/retest variability of your assay? In other words, 100 percent are getting one grade and they are starting most often at minimal pigmentation. What is sort of the chance of detecting a change when it is not really there?

DR. BEDDINGFIELD: Perhaps I could just get you to repeat the question. I am not sure I fully understood it.

DR. REPKA: In your electronic or digital analyses if you do it once and then do it again you will have some test/retest variability. You know, one of the endpoints here is 100 percent one grade improvement. Yet, that is most often seen when you start with minimal, grade 1 or grade 2. So, the bias there should be in detecting a difference if there is a high test/retest variability.

DR. BEDDINGFIELD: So, specifically your question is about the digital image analysis and the coefficient of variability on that. Perhaps I could call Bill Canfield up

PAPER MILL REPORTING  
(301) 495-5831

DR. REPKA: Miss Cofer?

MS. COFER: Hi, Paula Cofer. I assume Lumigan is only prescribed by ophthalmologists, is that correct?

DR. WHITCUP: For glaucoma it is currently prescribed by ophthalmologists. That is correct.

MS. COFER: So, my question is, is bimatoprost designed to be prescribed by ophthalmologists, dermatologists or other medical doctors? Could you clarify that? Then I have another question.

DR. WHITCUP: Sure. We think that this can be safely prescribed by non-ophthalmologists for a number of reasons, the contraindications are few and easily recognizable, such as an active eye infection, similar to a number of other eye products that non-ophthalmologists prescribe.

In addition, because the side effects are predominantly mild and reversible, we think we can get good instructions for all prescribers. And, as part of our program, we have very specific instructions not only for patients, which is critical, but also prescribers. So, we think with routine care non-ophthalmologists should be able to safely prescribe the product.

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

62

MS. COFER: My follow-up question to that is if the drug is prescribed by non-ophthalmologists how will the ocular exams be performed? I am assuming that the non-ophthalmologists don't have the tools to do some of the ocular exams that are required for prescribing the drug and follow-up.

DR. WHITCUP: So, we don't believe that a standard ophthalmologic exam is required to follow patients on the product. Clearly, it is a good point in the patient materials to have people get standard ophthalmic care but if they are not developing issues or if they haven't had surgery, we didn't see any effects on the eye that would require you to do an ophthalmic exam to find the side effects. It is mostly redness and irritation that standard care prescribers should be able to pick up. Most of them really the patient will be able to know.

MS. COFER: Specifically, I am interested in the intraocular pressure measurements. I don't know how a patient would know if they have elevated intraocular pressure or a non-ophthalmologist would know that.

DR. WHITCUP: So, I think the piece on intraocular pressure is the one we focused on the most. So, in our

PAPER MILL REPORTING  
(301) 495-5831

64

baseline, or is there a refractory period that they need to build up so that their follicles go into some state of needing to recover?

DR. WHITCUP: From the patients that we followed, they go back to baseline. So, they don't go to a lower level and then recover. They basically shed their lashes to get back to the baseline level.

DR. REPKA: Dr. Bilker?

DR. BILKER: I wondered if you could say something about the patient population in the study. Does this include any patients that lost their eyelashes or didn't feel comfortable with the look of their eyelashes due to disease, for instance cancer patients?

One of the reasons I am wondering about that is I noticed that in the vehicle group 20 percent of the population had a one grade increase in week 20 in their scale. So, I am wondering why it would be that high.

DR. WHITCUP: So, two questions there and maybe I will take the second one first. Because it was a static measure, if people were close to the next grade just with variability you could get one grade shifts. So, that probably explains the vehicle rate. It is one of the

PAPER MILL REPORTING  
(301) 495-5831

63

clinical trials we actually didn't see a clinically relevant change in intraocular pressure.

In discussions with the FDA, you know, we probably will have some information. If you are using Lumigan already or another drug in the class, you probably don't need to use this for eyelash growth. You should be getting the effect from the eye drops. The nice thing is that the bottles all have the same teal colored cap. So, in the patient education materials we will say if you are already taking a prostaglandin analog you may not need this. If you want to apply it directly, in those cases you probably should go see your eye doctor.

It is very easy to instruct the patient--you know, are you using one of these three medications available in the U.S.?--and the prescriber. So, we are heartened to see, despite intensive intraocular pressure testing, that we didn't see any meaningful change in pressure so we don't think that is a concern.

DR. REPKA: Dr. Afshari?

DR. AFSHARI: We are prolonging the anagen phase of the hair cycle and I was wondering once the patient stops this, the cilia shed and then does the patient go back to

PAPER MILL REPORTING  
(301) 495-5831

65

reasons why we looked not only at the 1 grade but, under FDA guidance, also looked at the 2 grade.

The other question is a great question that comes up, what happens to patients. For example, with chemotherapy patients can lose lashes. We only have antidotal data that actually those patients can regrow lashes earlier, and it is one of the things that the company is considering doing as the next step, looking specifically in disease states whether this could be a real benefit, for example, for cancer patients.

DR. BILKER: Are they included in this study?

DR. WHITCUP: I am sorry, they weren't included in this study.

DR. REPKA: Dr. Afshari?

DR. AFSHARI: Assuming that 100 percent of the medicine got in the eye and, of course, we know it doesn't and it is only five percent, and not necessarily that decreasing IOP would be a bad thing; it could actually be a good thing, but then from the Lumigan clinical trials how many points of IOP decrease did a patient have? Because potentially these patients could make a mistake and put it in the eye.

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

66

DR. WHITCUP: So, that is something that we looked at a great deal. We are fortunate, early in the development with glaucoma, to have actually treated normal eyes with Lumigan and usually the difference in pressure is, again, about 2 mm, sometimes 3 mm so, again, within the range of variation in tonometry, and we do not believe that even if they put the drop in the eye that would cause harm to the eye. So, another important point. Even if they put the full drop in the eye, we don't think that they would have intraocular pressure that would cause a problem. It is something that we have looked at a fair bit.

DR. REPKA: Do you know what the dropper is going to look like?

DR. WHITCUP: The bottle of medication, because we wanted to keep as much constant, proven and the same, the same model will be labeled differently. With guidance from the FDA, we are going to keep the cap the same color so people know, if they are on it for glaucoma and for the cosmetic, that it is the same class of drug. But it will be packaged with the sterile single use applicators. So, the dropper will be the same configuration, clearly labeled differently, but with sterile applicators.

PAPER MILL REPORTING  
(301) 495-5831

68

it was completely reversible.

Another interesting sort of anecdote is that, because it is only applied to the eyelid margin, some of the subjects who got skin hyperpigmentation actually appreciated it because it looked like an eyeliner but, again, it is completely reversible.

DR. REPKA: Over what time period was that reversibility experienced? You are going to have to use the glaucoma data there, I am sure.

DR. BEDDINGFIELD: The skin hyperpigmentation is an individual matter of how quickly it disappears. Sometimes it disappears within a few weeks and other times it takes slightly longer than that. We have not seen it be a permanent effect.

DR. REPKA: I have one other question. It regards what Dr. Wilson started to mention earlier, which has to do with the demographics in this population. Like him, I was concerned that substantially we saw essentially no African Americans in the treatment group. But it has to do with your effect by race or by ethnicity. If you could comment on that at least in the subgroup analyses that you didn't present here and I didn't see in the briefing binder.

PAPER MILL REPORTING  
(301) 495-5831

67

DR. REPKA: Scott, I have another question. Actually, it is probably more likely for Dr. Beddingfield. It has to do with the skin hyperpigmentation. We focused a lot on the lashes here because that is the main task here, but there have been, both with Lumigan and the BEG 032, a number of patients with skin hyperpigmentation. What is your experience? I am simply not familiar with what happens to this side effect long term.

DR. BEDDINGFIELD: For the skin hyperpigmentation we certainly can rely, in addition to the eyelash growth data, on the glaucoma data because, as you saw from the drop, a drop in the eye actually gets all over the lids and you are exposing the eyelids to a much greater amount, and those rates in the long-term studies are between 6-7 percent, and that is very reversible upon stopping the medication for glaucoma.

Now, the nice thing about the eyelash growth trial is that by reducing the amount applied and applying it only specifically to the eyelid margin we were able to reduce that to an amount that was no different than vehicle. In absolute terms it was 2.9 percent versus 0.7 percent in the vehicle group and those two were not different. And, again,

PAPER MILL REPORTING  
(301) 495-5831

69

DR. WHITCUP: So, given that same finding that we noticed, we spent a fair bit of time looking first in the glaucoma data set. So, when we compared both adverse events, specifically looking at things like skin hyperpigmentation and then eyelash growth, we didn't see meaningful differences between race. So, skin of color versus Caucasian were the same.

For the pivotal trial, although we only had one African American who was randomly assigned to vehicle, we did have 20 percent of non-Caucasians and, again, we looked at a subset of the primary analysis and so by efficacy there was no statistically significant difference in eyelash growth for Caucasians and non-Caucasians.

DR. REPKA: No statistically significant difference, but was there a difference that we ought to hear?

DR. WHITCUP: For example, there was never more than I think three to four percentage point difference one way or the other, so pretty meaningful. In the pivotal study some of the race subsets were very small so percentage-wise you might see a difference but I believe, for example, for safety in the pivotal study there was no

PAPER MILL REPORTING  
(301) 495-5831

adverse event that was more than one or two patients, and so no meaningful differences.

DR. REPKA: Dr. Afshari?

DR. AFSHARI: Can you say WHAT was the peak action time for a patient to have the maximum growth of their eyelashes, and then would the expectation be for the patient to continually take this medicine forever?

DR. WHITCUP: So, we usually see the eyelash growth plateau at about three to four months. That is both from glaucoma trials and from direct application to the eyelid. Again, if you stop using the medication, in about four to six months you go back to baseline. So, it depends on whether the patient wants to maintain the effect. If you do, then you probably will need to use this long term.

DR. AFSHARI: And have there been patients who have taken the medicine on and off, and on and off a few times?

DR. WHITCUP: Yes, from our glaucoma studies there clearly have been patients who have been put on the medication. They get the eyelash growth. They come off. Four to six months later the eyelashes go back to baseline and later they have gone back on the medication and get the eyelash growth once again.

PAPER MILL REPORTING  
(301) 495-5831

in the Division of Anti-Inflammatory and Ophthalmology Products, and I am the medical officer for this application so I will be presenting today.

[Slide]

As we all know, the applicant is Allergan, Inc. Much of the information that I will be presenting has already been presented so I will try not to dwell on anything that we have already heard.

[Slide]

As we know, the product that we are discussing is bimatoprost, which is a synthetic structural prostaglandin. Bimatoprost ophthalmic solution was approved in March of 2001 as Lumigan, in NDA 21-275, for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

[Slide]

The applicant's proposed indication is to improve the prominence of natural eyelashes as measured by increases in growth, fullness and darkness.

[Slide]

The proposed proprietary name is Latisse. The established name is bimatoprost ophthalmic solution. This

PAPER MILL REPORTING  
(301) 495-5831

DR. AFSHARI: Thank you.

DR. REPKA: I would like to thank the panel for their questions this morning. Thank you for the presenters.

We will now take a 10-minute break. Panel members, please remember that there should be no discussion of the meeting during the break amongst yourselves or with any member of the audience. We will resume at 1:25.

[Brief recess]

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

FDA Presentation

Division of Anti-Infective and Ophthalmology Products:  
Advisory Committee Meeting for Bimatoprost Ophthalmic  
Solution for the Treatment of Hypotrichosis  
of the Eyelashes

DR. LLOYD: Good afternoon, everyone.

[Slide]

I am Rhea Lloyd. I am one of the medical officers

PAPER MILL REPORTING  
(301) 495-5831

application was designated a priority review because this is the first application that we have received for this proposed indication.

[Slide]

First I am going to discuss the clinical studies for the ophthalmic indications for bimatoprost that have been submitted to the FDA to date. In NDA 21-275 for Lumigan, as the applicant has said, there have been four dose-ranging studies that were single and multicenter studies, double-masked, randomized, parallel, active and inactive controlled.

Additionally, for this NDA there were two safety and efficacy studies, the 008 and 009 studies that they have already discussed, which were also multicenter, double-masked, randomized, parallel group and active-controlled studies. Lumigan was approved in 2001.

[Slide]

For this particular application there have been three studies. They discussed the proof of concept, the open-label safety and efficacy trial, that they performed first to determine if this was a direction, I guess, they wanted to go in.

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

The 003 study was a validation of the Global Eyelash Assessment scale that they developed to measure eyelash prominence. As they also said earlier, the objective of that study was to evaluate the inter-rater and intra-rater reliability of the photo numeric that they developed.

The last study, the 032 study which is a safety and efficacy trial, is the trial that I will be reviewing here today.

[Slide]

The objective of that Phase 3 trial was to evaluate the safety and efficacy of bimatoprost for the eyelash growth indication when applied once daily compared with vehicle.

[Slide]

It was multicenter, with 16 sites, randomized, double-masked and parallel group, with a vehicle control. The subjects were instructed to apply one drop of the study medication to a disposable single-use-per-eye applicator with a brush along the upper eyelid, as they discussed, once daily in the evening.

[Slide]

evening through month four. There were follow-up visits at months one, two and three, and their primary efficacy endpoint was at the end of week 16, month four. There was no dosing for month four through month five, and there was a post-treatment visit at the end of month five.

[Slide]

As they discussed earlier, they developed this Global Eyelash Assessment photo numeric guide which they used to assess eyelashes in the subjects. It was a static assessment, as they have already discussed, of the overall bilateral upper eyelash prominence, and it was a four-point ordinal scale, as has already been discussed.

[Slide]

I have some sample photos of subjects with grade 1 and grade 2.

[Slide]

Grade 3 and grade 4. You have seen similar photographs earlier.

[Slide]

Their protocol defined analysis populations were an intent-to-treat population which included all randomized subjects, regardless of whether or not treatment was

The key inclusion criteria are that the subjects were greater than 18 years of age and they were dissatisfied with their overall eyelash prominence.

They had screening and baseline GEA score of 1 or 2, 20/100 or better visual acuity, with IOP that was within normal range, less than or equal to 20 mmHg in each eye, and an acceptable quality standardized eyelash photographs could be obtained.

[Slide]

There were many exclusion criteria. Just briefly, the exclusion criteria generally were to exclude people with uncontrolled systemic disease, without visible or with asymmetric eyelashes, with any diseases or abnormalities of the eyelids or ocular adnexa, with any conditions that would confound their measurements, any active ocular disease, any surgery during the three months prior to entry into the study, and any other aesthetic procedures to their eyelashes, permanent eyeliner or eyelash implants or dyes.

[Slide]

The study design was, after patients were randomized and enrolled into the study, the first dose began the evening of day one. They dosed once daily in the

received or administered; a per protocol population of all randomized subjects who had no major deviations from the protocol; and a safety population, all subjects who received one or more doses of the study medication. If a subject was given the wrong study medication, the analysis of the subject's data was based on the actual treatment that they received.

[Slide]

This is just a slide with the demographics and baseline characteristics of the ITT population. It is pretty much just to show you that the treatment groups were pretty equal. There were significantly more women than men enrolled in the study. That is what we wanted to show you with this slide, for the most part.

[Slide]

Subjects who discontinued the study are shown here. In the bimatoprost group 131 people completed the study compared with 126 in the vehicle group. The total discontinuations were six in the bimatoprost group and 15 in the vehicle group.

[Slide]

The analysis populations were essentially the same

ProTEXT Transcript Condensing for Windows

as those enrolled in the ITT and safety populations. Our per protocol population included only observed cases so we had 131 patients in the bimatoprost group and 126 in the vehicle group.

[Slide]

Again, this slide just shows subjects who were discontinued. As they said earlier, the subjects who discontinued that treatment had four in each group. The patient with xerostomia did not discontinue the study but discontinued treatment. Additionally, there were discontinuations due to loss of follow-up, protocol violations and subject decision, which were predominantly subjects in the vehicle group.

[Slide]

The primary efficacy variable of this trial was a change in the GEA score from baseline to the measurement at week 16, and clinical success, as we have discussed, was at least a one-grade increase from baseline.

[Slide]

This chart shows the percentage of subjects with a greater than one-grade increase from baseline during the treatment and post-treatment periods. We can note here that

still significantly different than the vehicle groups.

[Slide]

Three secondary efficacy endpoints were evaluated by the applicant and they were eyelash length, progressive eyelash thickness/fullness and overall eyelash darkness/intensity, as they have already discussed.

[Slide]

They were also determined by image analysis of digital eyelash photographs from the superior view across both eyes.

[Slide]

The first one is eyelash length. This was measured within a defined eyelash boundary for each eye, which they called the full area of interest. That area of interest was divided into a series of 25 vertical pixel segments. The maximum upper eyelash length was defined as the maximum height of each segment within each of these segments and it was measured in pixels and in millimeters.

[Slide]

In this chart I used the per protocol population to show the change in mean eyelash length, the mean change from baseline to week 16 which was the primary endpoint.

the difference between the treatment groups in subjects with greater than one-grade increase became statistically significant at week eight and remained statistically significant at the primary endpoint and through the post-treatment period.

[Slide]

We also did the same table but with a greater than two-grade increase, like we were just discussing. The greater than one-grade increase could be noise, as the applicant was discussing, and this is greater than two-grade, and we can see that at week 12 the difference between the treatment groups becomes statistically significant and that also was maintained through the primary endpoint and the post-treatment period.

[Slide]

This is the same information but in a graphical form. The red bars are those subjects who had a greater than one-grade increase. The green is greater than two-grade increase and the blue and the yellow are the vehicle groups.

So, you see that greater than one-grade increase is much greater than vehicle and the two-grade is less but

Treatment ended at week 16. This difference was statistically significant, less than 0.0001. All of the secondary endpoints met that statistical bar. We see that the eyelash length during the post-treatment period levels off, as they discussed.

[Slide]

The next secondary efficacy endpoint was progressive eyelash thickness and fullness. Again, they evaluated three preset rectangular areas along the upper eyelashes, proximal, medial and distal, I guess, relative to the eyelid itself, and at fixed distances from a standardized point.

For each superior view image the number of pixels representing the upper eyelashes was counted within that preset rectangular area. An average of the three rectangular areas was taken. This measurement was given in millimeters squared.

[Slide]

Again, this chart shows progressive eyelash thickness/fullness and mean change from baseline and the percent of the area of interest. At week 16 the primary endpoint again was significant at the p less than 0.0001

ProTEXT Transcript Condensing for Windows

level. It is again interesting to note that during the post-treatment period where patients were not dosed this value fell off just a bit.

[Slide]

The last secondary efficacy endpoint was overall eyelash darkness and intensity which was determined by eyelash intensity of the upper eyelash area within the spline, which was a line that went through this area of interest.

The darkness or intensity of each pixel blob along that line was reported as a mean intensity of the red, green and blue scale. The mean intensity of each pixel blob was then interpreted on an eight-bit image gray scale on a continuum, with 0 being black and 255 being white. So, mean lash intensity was the average intensity of all the pixel blobs. Again, it was calculated within the full area of interest.

[Slide]

These numbers show a mean change from baseline. If the lashes are getting darker this number should become more negative. So, in the bimatoprost group, which is in red, we see a significant difference at the week 16 time

Phase 3 studies there were two studies, again with QD and BID dosing, both of which were for a 12-month duration, bimatoprost in combination with timolol, two studies, also each for 12 months and Lumigan studies in the published literature, each for six months in duration.

[Slide]

And, a Phase 4 marketing study which was three months, and bimatoprost studies for eyelash growth, the first one for three months and this one that we have been reviewing, the 032 study, for four months.

[Slide]

The review of the safety study for this study, 137 subjects were on bimatoprost. The mean duration of treatment exposure during this study was 113 days. The majority of subjects were exposed for at least the entire 16 weeks, which is 73 percent.

[Slide]

There were no deaths during the study. There were three nonfatal serious adverse events, one in the bimatoprost group which was a squamous cell carcinoma on the back of one patient. In the vehicle group there was a lymphoma and recurrent metastatic breast cancer.

point versus vehicle. Again, this had the same statistical significance as the two previous secondary efficacy endpoints. During the post-treatment period the darkness falls off as well.

[Slide]

I will move on to safety now. The exposure data for bimatoprost ophthalmic solution, as has already been discussed, is taken from the Lumigan data, NDA 21-275, and following that approval, as well as the data presented for the eyelash growth indication.

There were two Phase 3 trials in support of Lumigan; a Phase 4 Lumigan marketing study; Lumigan postmarketing data; published literature studies of Lumigan; and the two trials for eyelash growth.

[Slide]

Bimatoprost alone or in combination has been evaluated in over 1,500 patients for over one year, and this is when applied directly to the eye or into the eye. We consider that a worst case scenario for this indication, so that provides very good safety data for this indication.

[Slide]

Again, reviewing those studies, for the Lumigan

[Slide]

This just shows the different adverse events that occurred in the two groups that led to study discontinuation. They have already been reviewed. In the bimatoprost group, eczema, dry eye, and eye inflammation which was a post-cataract CME and contact dermatitis. Then, xerostomia in the vehicle group, as well as lymphoma, eyelid erythema and conjunctival hemorrhage and low IOP in the vehicle group.

[Slide]

This is just a chart that shows the adverse events reported by greater than one percent of subjects during the treatment or post-treatment period, combined. Again, we just show the conjunctival hyperemia and eye pruritus, both of which were about 3.6 percent, five patients in the bimatoprost group.

Another interesting thing about this slide is that the safety profile, or the adverse events that are reported, are very similar to, just about identical to those that were seen in the Lumigan trials, the skin and subcutaneous tissue disorders, skin hyperpigmentation and contact dermatitis also of the periocular skin.

Usually we talk about postmarketing experience with the drug that we are discussing. Of course, Latisse has not been marketed yet but Lumigan, which is the same drug product has. So, as has been reviewed for the Lumigan postmarketing experience, there have been 2,410 case reports submitted, 5,000 adverse events. The most frequent reports are for conjunctival and ocular hyperemia, eye irritation, skin hyperpigmentation and eye pain, and growth of eyelashes also in there, 189.

[Slide]

That concludes my presentation. The questions for the advisory committee will be do you think the benefits outweigh the risks for Latisse, bimatoprost ophthalmic solution, for the treatment of hypotrichosis of the eyelashes?

If not, what additional studies should be performed? If yes, should any additional Phase 4 studies be performed?

Do you have any suggestions concerning the labeling of the product? Thank you.

Questions/Clarifications

DR. REPKA: Are there questions from the panel for

PAPER MILL REPORTING  
(301) 495-5831

question was once you go and make these changes, are you reconfirming what you have already seen, and we thought that could be done with one trial.

In addition, as you see the different p values that are here, you can split this any way you want in a number of different trials and it always looks statistically significant.

DR. LAVIN: I guess my question was, was the powering intentionally done with this trial, planned, like, with 95 percent or 99 percent power because you knew that the study endpoint was going to be, you know, so dramatic?

DR. CHAMBERS: I will let Allergan answer why they powered the study with that particular thing, but you also have to remember we did want some minimal database, at least, of using it in this particular configuration. So, even if it takes ten patients, we would not want a trial that was only ten patients, even if that is all that it takes to go and show the efficacy.

DR. WHITCUP: This is Scott Whitcup. Just to echo Dr. Chambers' point, we powered it based initially on the glaucoma database but, knowing that we were specifically measuring eyelash growth, we knew that the actual power

PAPER MILL REPORTING  
(301) 495-5831

Dr. Lloyd? Dr. Lavin?

DR. LAVIN: I have a couple of questions. Normally I am used to seeing two pivotal studies. For example, we saw that this morning. What was the thinking behind one pivotal study here, and also how was that powered? That is the second part of my question.

DR. LLOYD: The thinking behind one pivotal study here is that this is the same drug product as Lumigan. We know that it is safe and efficacious for reduction of intraocular pressure indication, and we know that this was seen in those pivotal studies. When we expand an additional indication we usually just require one additional study. Do you have anything to add, Dr. Chambers?

DR. CHAMBERS: Wiley Chambers. It varies from indication to indication whether we ask for one or two. But if you noticed in Allergan's presentation earlier, there was a statistically significant increase in eyelash growth in the earlier trials so you already have evidence of this phenomenon occurring with this product, just administered a slightly different way.

So, we basically viewed it as the formulation being the same but a different administration. So, the

PAPER MILL REPORTING  
(301) 495-5831

might be greater. But in discussions with FDA, we wanted to have enough patients exposed to have additional safety as well. So, in the end we ended up with very highly statistically significant results but we didn't necessarily power it that way. We wanted to have a study that had robust numbers for safety and for efficacy.

DR. LAVIN: So, I guess the sample size was driven off of the safety considerations, not the efficacy. Is that what I am hearing?

DR. WHITCUP: Predominantly for safety, although we wanted to make sure, even if the rates were what we had seen in the glaucoma studies where we think it was slightly under-reported, that we would be sufficiently powered, but mostly driven by safety and having a robust database.

DR. REPKA: Miss Cofer?

MS. COFER: My question is actually on sort of a follow-up to the question I had for the sponsor but it came up again in this presentation, and it is about the non-ophthalmologists. I am looking back at my notes and there were some non-ophthalmologists in the clinical trials for this indication.

So, my questionB-and I don't mean to sound like a

PAPER MILL REPORTING  
(301) 495-5831

broken record but I just don't understand how the inclusion and exclusion criteria tests were performed if they were performed by a non-ophthalmologist. So, I just need some clarification on that.

DR. LLOYD: How the inclusion and exclusion could be determined by a non-ophthalmologist? Is there a specific one that you are referring to?

MS. COFER: Yes, I am looking, in the inclusion criteria, best corrected visual acuity equivalent to Snellen 20/100 or better in each eye; intraocular pressure less than 20 in each eye.

DR. LLOYD: I can explain that. Although some of the investigators were not ophthalmologists, ophthalmologists were available at each study center to perform those tests for the inclusion and exclusion criteria. That wouldn't be necessary if you were prescribing to a healthy individual but, for the purposes of the study, even if there was a non-ophthalmologist who was the investigator, an ophthalmologist was available to do those tests.

Open Public Hearing

DR. REPKA: Thank you, D. Lloyd. I think rather

PAPER MILL REPORTING  
(301) 495-5831

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

At present we have one speaker signed up for the open public hearing session. We will go to that speaker now. That would be Brandel France de Bravo, from the National Research Center for Women and Families.

MS. BRANDEL: Good afternoon. I just want to open my statement by thanking everybody today, the advisory committee for allowing me to speak.

My name is Brandel France de Bravo, and I am testifying on behalf of the National Research Center for Women and Families. Our Center is dedicated to improving the health and safety of adults and children, and we do that

PAPER MILL REPORTING  
(301) 495-5831

than go to a break, we are going to continue forward and go on to the open panel hearing.

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 an open public hearing session of the advisory committee meeting FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship you may have with the sponsor, its products and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of you statement it will not preclude you from speaking.

PAPER MILL REPORTING  
(301) 495-5831

by scrutinizing the medical and scientific research to determine what is known and not known about specific treatments and prevention strategies, and to compare their safety and effectiveness.

I have a masters in public health from Columbia University and two decades of experience in international and U.S. health programs, including HIV-AIDS prevention, reproductive and maternal child health, and harm reduction for drug users. I have designed, conducted and analyzed research, as well as developed health education campaigns using a variety of media. Other than suddenly discovering that I may have a condition called hypotrichosis of the eyelashes, I have no conflicts of interest.

Last month the FDA held an advisory committee meeting on wrinkle fillers that is relevant to today's meeting. A key question was should the standards for approval for a product whose benefits are cosmetic be different than the standards for a product with medical benefits. Everyone on that FDA panel agreed that the standards should be more stringent when the benefits are cosmetic to make sure the benefits outweigh the risks.

Frankly, we at NRC for Women and Families are a

PAPER MILL REPORTING  
(301) 495-5831

little disappointed that the research presented today for Latisse is skimpy so we have five major concerns we wanted to just bring up.

Number one, the study used a very small sample size. Number two, the data are too short-term and, yet, we assume that anyone who wants thicker eyelashes will continue to want longer, thicker eyelashes for many, many years. Unlike many real diseases, hypotrichosis of the eyelashes doesn't go away. There is no permanent cure. For that reason, we need longer-term data.

Three, only one African American was included in the study. Four, the adverse reactions weren't described in enough detail. How long did the eye itching and other eye irritations last? How long did the discoloration of the whites of the eyes last, and how unattractive was it? Although some adverse reactions are from the vehicle rather than the active ingredient, they are still problematic since the product includes the vehicle in addition to the active ingredient.

Lastly, when the same product is used for glaucoma under the name Lumigan the company warns that it can permanently change eye color, usually from light colored to

PAPER MILL REPORTING  
(301) 495-5831

eyelids day after day, month after month, and year after year.

Allergan has publicly stated its intention to widely advertise this drug as soon as it is approved by the FDA. As everyone here knows, the adverse reactions are in tiny print in magazine ads and are often not even mentioned on TV ads. Do the benefits of this drug outweigh the risks?

Is informed consent likely for most of the women who will see the ads for this product? We believe the company has not proven that. Therefore, this product should not be approved. Thank you very much for hearing me.

DR. REPKA: You are welcome. Other comments for the open public hearing from the audience? Hearing none, the open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience.

#### Panel Discussion/Questions

DR. REPKA: The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. We will now begin the panel discussion portion of the meeting. Although this portion is open to

PAPER MILL REPORTING  
(301) 495-5831

brown. The change in the color of the iris is gradual. It can take months or even years for blue, green or hazel eyes to turn brown.

Now, the Latisse study was carried out to only 20 weeks. Change in eye color is an adverse reaction that is acceptable to someone trying to prevent blindness from glaucoma but is probably not acceptable to someone using the product to improve their eyelashes.

Allergan presumably hopes that this won't happen since Latisse is intended to be applied to eyelids and not eyes, but I think it is safe to assume that sometimes some of this product will get into the eyes and, again, it may be used for years. So, if this product gets only into one eye and not the other the person using Latisse may end up with one blue eye and one brown.

We know something about the safety of Latisse based on slightly larger studies of the identical drug when it is used for glaucoma. The pharmacological category is prostaglandin analog, which is described as, quote, a potent hormone-like substance. As a potent product, that is, one that can change eye color or skin color, we need research that can tell us what the effects will be when applied to

PAPER MILL REPORTING  
(301) 495-5831

public observers, public attendees may not participate except at the specific request of the panel. Dr. Wilson?

DR. WILSON: As a glaucoma specialist, I am familiar with the glaucoma literature, and also from my clinical experience, I do want to emphasize that I have absolutely no reason to question the efficacy or the effect of Lumigan on eyelid growth. I also want to emphasize that I don't have any concerns whatsoever about the potential side effect of the drug on the eyelid, even with respect to race specific side effects and race specific effects.

However, having said that, I do take issue with the conclusion drawn from the single study on the efficacy summary that there were consistent results across age and race. I think the preponderance of evidence would suggest that to be the case and I am comfortable with that, but looking at this one single study, the data is not there to make that kind of conclusion.

Personally, I think this should be more generalizable to a more representative population. Nonetheless, the study was done in the way it was done and I just want to, again, emphasize that I have no question about the actual statement that was made, but I do question the

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

98

actual statement being made on the basis of this one study.

DR. REPKA: Other comments? Dr. Miller?

DR. MILLER: I think that the data shows an effect and we have seen this with Lumigan. I take care of patients which were not in this study where they have absence of lashes for various medical conditions, and my ultimate interest is more on that line than a cosmetic line in my type of practice. But I take care of kids and I am worried about off-label, non-supervised use of this medication as we work through our further discussion and concern that the teenagers might use this three, four times a day kind of thing.

I don't know what our role is in preventing this.

We are deciding whether this drug is safe or not as we want to give it or as we are telling people to give it, and I think that is something I feel comfortable with for adults for this particular application, but it is a medication that will be used by some people outside the label. What is our role for thinking of that?

DR. REPKA: Dr. Chambers?

DR. CHAMBERS: This is Wiley Chambers. Since the label hasn't been written it is not necessarily off-label

PAPER MILL REPORTING  
(301) 495-5831

100

opinion about what age the product should be labeled down to if it is approved, and on what basis to draw that particular age.

Do we then unnecessarily exclude people who for a disease component have that, which we might not want to do?

We also have the option of asking for Phase 4 studies or, if ultimately not approved, Phase 3 studies that are in a pediatric population if that is what the recommendation of the agency at that point in time is. And, as I said, we have not achieved a consensus. We are very much open to the opinions of the members of the committee on which way to go.

DR. REPKA: Dr. Miller?

DR. MILLER: If this is approved for use in adults, I would actually think of several patients, a couple of patients per year, that I would want to try this medication on that are children because they have no lashes for various reasons. So, I wouldn't want the labeling to exclude that because I don't think that the data shows me that it is not safe, in my own mind. On the other hand, it is those teenagers substituting it for mascara that would concern me and I don't know how to work around that.

DR. CHAMBERS: This is Wiley Chambers. We are

PAPER MILL REPORTING  
(301) 495-5831

99

and it is one of the questions that we remain undecided on within the agency.

In particular, I am referring to the part of the pediatric legislation that has been written within the Food, Drug and Cosmetics Act that calls for a pediatric plan for all drugs. That includes, obviously, this product. The question remains exactly who should this be prescribed for or what should the label say as far age group. The particular studies that were done at this point in time were 18 and above. While we can potentially approve a product because the product has shown safety and efficacy in adults and the pediatric plan has not yet been completed, we do need to have a pediatric plan.

That does not necessarily mean we need to study it in pediatric patients. We can say that there is a safety problem and waive the studies in pediatric patients and label it because there is an X safety problem. We have not identified a safety problem for this particular product to implement that and waive it. We have had debates about what age we should recommend and/or exclude within the product labeling and we have not achieved a consensus.

We are very much interested in the committee's

PAPER MILL REPORTING  
(301) 495-5831

101

envisioning this as a prescription product so it would require a prescription and will require the intervention of a physician. Not that this diagnosis is not self-diagnosable. We believe that it is self-diagnosable, but there are various labeling concerns that we think should be included within the labeling and there should be a discussion with a physician before it is prescribed.

That does not necessarily preclude it from being used in a particular age group and, while I may have personal views of what age is appropriate to use for cosmetic indication, that does not necessarily mean it is scientifically based and we are looking for a scientific basis to try and make those determinations.

DR. REPKA: Miss Cofer?

MS. COFER: Paula Cofer. I had some of the same concerns that the speaker from the Center for Women and Families had with regard to the small sample size and short duration of the study for this indication, African Americans not being represented in this indication for the drug, and the risk of iris pigmentation. So, I did have some concerns about those things.

I said earlier I don't want to sound like a broken

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

102

record but I am going to now. If we polled the people in this room, my guess is that 100 percent of the people in this room that would like to try this drug to increase eyelash growth would prefer to be screened and followed by ophthalmologists because when you are talking about your eyes and your vision, that is so important to quality of life and I just don't think we can stress safety enough in that regard. And, I don't know if the FDA can address that.

DR. REPKA: Dr. Chambers?

DR. CHAMBERS: Wiley Chambers. Our basic mechanisms to provide information, assuming the product is approved, are to put labeling statements in and it is certainly our intention, if the product is approved, to put in the various statements that the product will potentially increase iris color; that there are issues with using another prostaglandin analog and this product as far as getting the effect you would expect to from a prostaglandin.

As was presented by Allergan, if you use a prostaglandin more than once a day you don't have as effective a product as using it once a day. Whether that ends up being for eyelash use or other, it is likely some is going to get into the eye and will decrease the effectiveness. So, all those

PAPER MILL REPORTING  
(301) 495-5831

104

DR. MAJUMDER: I just had a question concerning Phase 4 studies. I have only been to one prior committee meeting but there was some frustration expressed about the track record in the past in terms of completion of Phase 4 studies. Can you make any kind of general statement about current rates of compliance when those sorts of commitments are requested?

DR. REPKA: Dr. Chambers?

DR. CHAMBERS: This is Wiley Chambers. The history on Phase 4 studies is mixed in different parts of the agency, and I am only going to speak about it within the ophthalmology group because that is what I have had some jurisdiction over, and it is very good in the ophthalmology group.

There are a number of reasons for that. Some of them I personally believe are because I take a personal interest in it and it is not that big a community, and there are a number of companies that know that when we have asked for a Phase 4 commitment and they then come in for something else, if the Phase 4 commitment hasn't been completed that is the first question that gets asked. It is, where are you on the Phase 4 commitment? So, our track record within

PAPER MILL REPORTING  
(301) 495-5831

103

need to be monitored.

As far as being studied in the appropriate population, this would not be the first product that had not necessarily had a complete representation of the U.S. population at the time that the studies were submitted. And, having one patient not even in the treatment group in the African American population I would suggest is not representative of the U.S. population.

We have in the past required Phase 4 studies that looked at populations that were missing. And, I am open to comments about whether we should do that or not, but I am just telling you what we have done in the past. We have in a number of cases approved a product and then required additional trials to get that information, particularly when there was some suggestion it wasn't going to be a problem but we wanted confirmation in actual patients.

If this is not a big enough safety database, then the question we would ask is what is so that we can provide additional guidance to the company about what would be a sufficient database to be able to make the assessments of safety and efficacy.

DR. REPKA: Dr. Majumder?

PAPER MILL REPORTING  
(301) 495-5831

105

ophthalmology is very good in getting them completed and we do follow up.

DR. REPKA: Dr. Wilson?

DR. WILSON: I think it is a mistake to ignore or minimize the many volumes of data that you have for many, many years on the use of this medication for glaucoma. I can't think of a physiologic mechanism that makes me think that applying the medication on the lid is somehow going to be any different than medication getting on the lid by using the eye drop.

This is in answer to your question now, Wiley, about the Phase 4. I don't see any reason for going into a Phase 4 given all the volume of data that we already have on the effect of this medication.

The fact that there was only one African American in the study, I think it is a poor study design as a result of that. I mentioned that. However, again, I think it is erroneous to ignore the volume of data we have using the glaucoma medication Lumigan. Again, you would have to surmise some sort of physiologic mechanism for why applying it in one way is going to be different than application another way, and I just can't think of it.

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

106

The other point that was made is this thing about being followed by an ophthalmologist. You know, presumably these subjects or these patients are going to have their usual standard of care and some of them will be seeing an ophthalmologist and some of them will not.

You know, I personally, again, don't see a reason why a person needs to see an ophthalmologist to be followed for something that is being applied on the lid. But if there are these warnings that are going to be put in the product label, and if it causes some people who are not being followed by an ophthalmologist to get their eye check, I think actually that is more of a public service than the other way around.

DR. REPKA: Let me ask about the packaging. Since it is going to be in the same bottle will there be ways pricing will, in fact, drive people to use it improperly, or to use the Lumigan, for instance, for this application with some home-made applicators, and whether that is going to have any impact on the application? I realize that no agency can stop that, but you are setting yourselves up here with a product that looks the same and it won't take long on the Internet to figure that out.

PAPER MILL REPORTING  
(301) 495-5831

108

to get medication covered. Have you thought about that, or how you are going to approach payer side?

DR. WHITCUP: We have actually very good information on use for glaucoma and who is prescribing. It is something that is followed, not very well by us, but by payers. Again, you know, a physician would have to prescribe this for the wrong indication and take a fair bit of risk to do so. We don't see that, you know, really as a risk.

We, clearly, have enough focus on that and our glaucoma patients are, you know, part of our core reason for being so it is something that we will monitor closely. In talking with our reimbursement group they don't see that as an issue. It would require a physician really going in and taking a fair bit of risk, putting a false diagnosis on a patient record, which we can track, to do this. So, we think it will be, you know, rare or nonexistent.

DR. REPKA: Dr. Whitcup, in fact, I actually meant the commercial payer, the TPA or the pharmaceutical company sort of saying, well, we are not going to pay for bimatoprost anymore because it has a cosmetic indication. You can see at some level that happening, producing some

PAPER MILL REPORTING  
(301) 495-5831

107

DR. WHITCUP: Dr. Repka, that is something we have spent a fair bit of time thinking about. Since it is a prescription product and you do need a physician to write that, part of the prescriber information will clearly emphasize the fact that only the eyelash growth product has the sterile applicators. We also have ways of actually monitoring that. So, again, the postmarketing safety piece I think is very important for this as well, both to ensure patient safety and that it is prescribed as appropriate.

So, as part of our postmarketing safety surveillance we have a targeted questionnaire so for every case that comes in to us we determine who was the prescriber, what was the indication and what drug was used, the dose, age, race. So, some of the questions that have come up are things that we want to focus on as well post-approval.

DR. REPKA: Let me ask you a somewhat analogous but connectedB-it is not even an analogous question, but obviously if you create a pharmaceutical that will carry the same generic name there is the potential for confusion on the payer side in terms of coverage policy. In fact, we may see that patients for glaucoma all of a sudden are not able

PAPER MILL REPORTING  
(301) 495-5831

109

frustration within the provider and the patient community.

DR. WHITCUP: You know, I think it is an inappropriate concern to raise again because when we have talked with our payers, since they know and can track diagnoses and actual patient records with prescriptions, there is a very well-documented pathway and so the risk of physicians actually falsifying medical records to show that there is a diagnosis of glaucoma to go with the prescription is a fair deterrent to keep this, we think, at a low to a nonexistent rate, and that is something that, you know, we will be following closely.

DR. REPKA: Yes, I encourage you to because your company, of course, has another agent that has just that same problem and it does create a problem, certainly for payers in Maryland, to manage that differentiation.

DR. WHITCUP: You are absolutely right. We have experience with that and we will be vigilant as well with this.

DR. REPKA: Dr. Lavin?

DR. LAVIN: I would like to make one point. We have been down this path before, on this very panel, with minoxidil and Rogaine and the two are not at all confused.

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

110

If that is our track record, I think that should give some sense of security and comfort to everyone here, thinking that that problem hasn't been faced before because it has.

DR. REPKA: I agree. As I mentioned, it has actually been faced by this company before. Other questions or comments by the panel?

[No response]

Then I think we are prepared to vote on question 1, do you think the benefits outweigh the risks for Latisse, bimatoprost ophthalmic solution, 0.03 percent for the treatment of hypotrichosis of the eyelashes?

Let me comment that we are going to come back to questions 3 and 4, some of which we addressed here for further discussion, subsequent to this question. Please push the button to vote, those of you that are allowed to vote.

[Electronic voting]

Thank you. The voting result for the record, yes, 9; no, 0; abstain, 0. We will go to the voting record for placing reason on the record. I think we will start in reverse order from the bottom. Dr. Wilson?

DR. WILSON: I voted yes, particularly because of

PAPER MILL REPORTING  
(301) 495-5831

112

DR. REPKA: Thank you. Dr. Lavin?

DR. LAVIN: I voted yes from a clinical trialist perspective. First, I think that they got to this point through a very carefully staged and thought out series of experiments and studies, namely, to be able to go and do the DIA work was important, but also to do the validation of the GEA. That was equally important and I think that set a great, you know, foundation. Also, they are looking at their data and mining it and following up their patients, and having the foresight to have the registry in place for the glaucoma patients. That was also fortuitous.

Also, I think this is a trial that by any calculation has over 95 percent power to see any kind of 25 percent improvement, whether it is the one-unit improvement or the two-unit improvement. A trial that has that kind of power really has done, I think, a great service to making people feel comfortable with the efficacy and the safety.

Then also, those improvements which were seen are visually identifiable as improvements so that I contend that 70-80 percent of the population can see an improvement as a result of being on this therapy and that is something that is a very high hurdle.

PAPER MILL REPORTING  
(301) 495-5831

111

the preponderance of data on this medication for use in lowering intraocular pressure in glaucoma, and the fact that it is spilled over on the lid and there is a lot that is known about this.

DR. REPKA: I am next. I voted yes for basically the same reasons, the track record. The information in the glaucoma population across a pretty wide age range has been quite successful, though I did mention, and will in subsequent comments discuss the ethic, racial mix in future follow-up. Dr. Miller?

DR. MILLER: I also was depending on the information of patient-year data for Lumigan which gives a lot of confidence for the safety with this. Clearly, there is an effect with this medication for the lashes. And, I think that as a prescribed medication we will have to think about the labeling and how the relationship with the physician and the patient keeps this drug used properly.

DR. REPKA: Thank you. Dr. Majumder?

DR. MAJUMDER: I voted yes because I thought however I might personally weigh the risks and benefits, the regulatory standard was met, and I also have some labeling concerns. So, we will get to that later.

PAPER MILL REPORTING  
(301) 495-5831

113

DR. REPKA: Dr. Gates?

DR. GATES: I voted yes. I am very comfortable with safety and efficacy of the product based on the Lumigan experience. As a general ophthalmologist treating lots of different conditions and lots of different patients, Lumigan or this particular product, bimatoprost, is not a drop that I feel like I have to hover over. It doesn't keep me up at night. There are other conditions, particularly HSV or monitoring patients on ocular steroids, that keep me up at night. I have to monitor those patients very, very closely. This is not that situation.

DR. REPKA: Thank you. Miss Cofer?

MS. COFER: I voted yes. The drug seems to be certainly effective and adverse events for the most part seemed to be non serious in nature and reversible with discontinuation of the treatment, with the exception of permanence of iris pigmentation. Again, I looked at the Lumigan trials that had a lot of weight in my decision to vote for the approval.

DR. REPKA: Thank you. Dr. Bilker?

DR. BILKER: I voted yes, and I felt that considering the previous studies on Lumigan and the study of

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

bimatoprost ophthalmic solution there was very strong evidence of safety of this product, and there was also strong evidence of efficacy.

DR. REPKA: Thank you. Dr. Afshari?

DR. AFSHARI: I voted yes because of all of the reasons that were stated and also because of the safety record of Lumigan.

DR. REPKA: Thank you. We will have the question list back, please. Given the affirmative answer to question 1, we will skip question 2 but move then to question 3. If so, should any additional Phase 4 studies be performed? That is going to be a voting question. Dr. Miller?

DR. MILLER: Dr. Chambers, can you state precisely for Phase 4 what they are again? The drug is approved and they proceed to be tested while the drug is approved and on market?

DR. REPKA: Dr. Chambers?

DR. CHAMBERS: Phase 4 just means that they would not necessarily be done prior to approval. The product could be approved. If there are additional studies they are still supposed to answer important questions. They are not supposed to be, well, we would just like to know this; here

PAPER MILL REPORTING  
(301) 495-5831

[No response]

So, let's vote on question 3, should any additional Phase 4 studies be performed?

[Electronic voting]

DR. REPKA: The voting results on question 3, affirmative or yes, 5; no, 3; and abstain, 1. I think we will start with the yes's. Dr. Afshari?

DR. AFSHARI: I said yes. Although I am very comfortable with the safety record of Lumigan, since this is a new indication, although we know that it works and the efficacy is fine, but then to track it over time, particularly for those younger patients to look at long-term iris pigmentary changes and any follicular changes over years and years of usage. I just want to make sure that there is no atypia developed over time from years of usage of this kind of medicine.

DR. REPKA: Thank you. Dr. Bilker:

DR. BILKER: I voted yes because I feel that there should be longer-term follow-up on patients, and also looking at different age groups.

DR. REPKA: Dr. Gates?

DR. GATES: I would like to see efficacy determined

PAPER MILL REPORTING  
(301) 495-5831

is an opportunity to get the drug company to do something that we would like to see happen as far as it is within science. They are supposed to be addressing particular issues with the product that we think are necessary for the safe and efficacious use of the product.

That said, there are fairly often unanswered questions in subpopulation or pediatric issues that we think ultimately will need to be resolved that have not been resolved. We have the ability within pediatrics to extrapolate down if we think the process is the same and say that, while it is not always the case, in this case the pediatric patient is a little person and they are going to react the same way. There are plenty of other cases where that is not true.

So, those are determinations that get made the same as potentially if there is some subset of a population that we think this may act differently in or some adverse event that we think needs to be particularly elucidated. Does that answer your question?

DR. MILLER: Yes.

DR. REPKA: Other comments before we go on to question 3?

PAPER MILL REPORTING  
(301) 495-5831

in the African American population.

DR. REPKA: Thank you. Dr. Lavin?

DR. LAVIN: I voted yes. I would also like to see that population, the people of color. I would like to see a small registry there of around 100 subjects. I would be interested also in seeing the long-term follow-up study as well, taking subjects out to perhaps a year.

DR. REPKA: I voted yes for a number of things I would like to see additional data on. First off, in fact, Dr. Chambers mentioned the potential of this in disease states and I think that that is a real likelihood that we are going to see, expansion from the well patient to the disease state, and at least some data collection on that group is in order.

I think because teens are going to use this drug by hook, crook or by any way we ought to look at that group specifically, or the sponsor should be asked to look at that group.

I think that data supporting the glaucoma data in races is necessary. I think that that would be an important thing to complete.

Then, lastly, the lower lid, the lower lashes have

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

SHEET 31 PAGE 118

118

not been mentioned in this application but I think it is inevitable that the patients will expand it to lower lids as well in spite of labeling. So, at least some information about lower lid should be begun to be obtained, or ways that you are going to be certain that it is not actually administered to lower lid.

We will go to the no's. Dr. Majumder?

DR. MAJUMDER: I was sort of swayed by Dr. Chambers in terms of wanting to know more about lots of questions but wondering if any of them sort of hit this standard. Also, I was thinking that some of our concerns might be met through a robust risk management program. So, I am certainly not averse to further studies, and I think there needs to be some way for some of these issues going forward.

DR. REPKA: Thank you. Dr. Miller?

DR. MILLER: As I mentioned previously, I am concerned about the teenagers. I would like to have this medication available for use in children with certain diseases. I see potential for it.

My understanding was that the company was planning a pretty robust tracking program so perhaps I was going to discuss in the labeling process the plan for tracking

PAPER MILL REPORTING  
(301) 495-5831

PAGE 120

120

questions for the committee? Question 4, do you have any suggestions concerning the labeling of the product? This is non-voting, though I suppose you vote by speaking. So, what should the FDA consider for labeling? Dr. Wilson?

DR. WILSON: Not for ocular application. The concern was being raised here earlier about people possibly putting it as a substitute for Lumigan inside the eye. That needs to be clear.

DR. REPKA: Dr. Majumder?

DR. MAJUMDER: I just think in the materials for the patients it needs to be very clear that they are not getting a lifetime of luxuriant lashes for a few applications. So, there is a pocketbook issue. Because it is an aesthetic use they will likely be paying and they need to know the limits in terms of needing to continuously use the product in order to maintain the benefit.

DR. REPKA: Miss Cofer?

MS. COFER: I would like to see something in the labeling in layman's terms about iris pigmentation because I am just not sure how many patients understand what that means. The worst case scenario would be you think your blue eyes are your best feature and then your eyes start turning

PAPER MILL REPORTING  
(301) 495-5831

PAGE 119

119

somehow. If you have to put teeth into that to do Phase 4 trials, then this is a no with yes, I agree, we have to follow long term.

DR. REPKA: Thank you. Dr. Wilson?

DR. WILSON: I think if we were making this decision on the basis of the study that was presented there is no question that further studies would be necessary, not even Phase 4 but Phase 3 studies. But, again, I am using the preponderance of data from many, many, many years and I just don't see any reason why this should be any different than Lumigan spilling over the lids, and I just think that there has got to be substantial and tough changes as mentioned in terms of the initial submission.

DR. REPKA: Ms. Cofer was an abstention. So, if you have comments?

MS. COFER: I abstained. I have no comments.

DR. REPKA: Thank you.

[Power outage.]

DR. REPKA: are we okay or shall we recess for a few moments? Why don't we take a five-minute break then.

[Brief break]

DR. REPKA: Why don't we go ahead with the

PAPER MILL REPORTING  
(301) 495-5831

PAGE 121

121

brown. I don't know if that happened or if that was seen in the Lumigan or the study. But I just think that needs to be very clear in the labeling, what that means, iris pigmentation, and the fact that that is prominent.

DR. REPKA: Dr. Miller?

DR. MILLER: Stating that the sister drug, Lumigan, has been tested in children but this particular application has not. I don't want it to say you can't use it in children but that more studies are ongoing, or some requirement that we have the ability to provide information on those patients when we see them. If I am going to give this to a five-year old, can I volunteer to give that information somehow with the labeling?

DR. REPKA: Marijean, how would you give it to five-year old?

DR. MILLER: Okay, so, say it is an eight-year old or ten-year old, but believe me, I could give it to a five-year old. No problem, as you know, we have lots of tricks but the typical family wouldn't give it to a five-year old.

But, you know, you have a kid who has had chemo and they are going back to school and they want to look more normal, and they already have no hair on their head, and you could

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

122

see a role for it.

DR. REPKA: Do we know it works with chemo?

DR. MILLER: We don't, but I really think it is something that needs to be studied. Does that mean we can't try it in kids where there is nothing? I mean, I have had patients come in begging me for something. We try steroids; we try antibiotics. There is nothing we can offer if they have no lashes or just broken lashes.

DR. REPKA: Dr. Afshari?

DR. AFSHARI: My thought is that some of those kids who don't have hair probably don't have that anagen phase of the hair cycle. I actually, I don't know. Probably dermatologists could answer that.

DR. REPKA: Dr. Beddingfield?

DR. BEDDINGFIELD: With respect to the use in cancer chemotherapy, this has not been studied formally. Anecdotally, there does appear to be efficacy and I think certainly there is reason to believe, on a scientific basis, that it can work. Unless the follicle is gone, there is potential for it to work in that population. In some other conditions where there is ongoing immune destruction it may not work as well. But in the cancer chemotherapy range

PAPER MILL REPORTING  
(301) 495-5831

124

ophthalmic oversight.

DR. AFSHARI: Right. So, I guess the question is let's say if a patient has a history of HSV keratitis, would it be okay to take this? Are we all okay to say, you know, only five percent would get in the eye? It would cause a little bit of hyperemia but it wouldn't cause reactivation so are we okay to have it in the eye? Probably so. As a corneal person, I would say probably so. Is that what the panel thinks? I am curious.

DR. REPKA: Does anyone know enough to comment on that? I mean, Lumigan in that setting? I don't. Dr. Wilson?

DR. WILSON: I wasn't going to comment on that but it did bring up a question. You know, how does even five percent get on the ocular surface? I don't understand that. When you put mascara on, does five percent of the mascara go on the ocular surface?

DR. REPKA: It depends on how heavily you are putting it on.

DR. AFSHARI: I think the only time is that we have the limitations in cornea with Lumigan or those types of medicine and we are cautious in those patients with corneal

PAPER MILL REPORTING  
(301) 495-5831

123

where the follicle is, by and large, still present in most of the cases there is potential for it to work.

DR. REPKA: Dr. Lloyd, did you see any drug interactions? I don't know of any with Lumigan particularly but with the other ophthalmic agents are there any that we should be talking about in terms of labeling?

DR. LLOYD: There were no drug interaction studies here. With the other prostaglandins, if they are in use for a reduction of intraocular pressure, that will often be less effective if this is used concurrently. But other than that, no.

DR. REPKA: Dr. Afshari?

DR. AFSHARI: Another thing about labeling to consider is something about caution for patients who have ocular surface disease and to be seen by an ophthalmologist prior to usage of the medicine, or to have some kind of requirement if they use it.

DR. REPKA: So, how does the prescribing doctor recognize ocular surface disease? I mean, you are putting that risk or that detection on the family doctor who wants to prescribe this for their 30-year old patient. That is a hard one unless you go back to Miss Cofer's level of

PAPER MILL REPORTING  
(301) 495-5831

125

transplants. I suppose if a patient has those other corneal conditions I would be okay prescribing it, as a corneal person. Hence, the family practitioner should be okay as well possibly. I am curious if anybody has any other thoughts.

DR. REPKA: I was going to say it is almost the perfect patient we use Lumigan in, in the young kids who have had grafts where we are looking for something to treat the aphakic glaucoma.

DR. AFSHARI: We just observe the corneal surface more in case there is an epithelial problem but I agree for glaucoma control it is great.

DR. REPKA: Dr. Miller?

DR. MILLER: So, are you saying that if they have a preexisting known corneal transplant they should continue with their follow-up with their ophthalmologist? I mean, they already have an ophthalmologist, right? I mean, they should. If they have a family history of certain diseases or herpes on the lids, I mean, can we think of anything where we say they have to see an ophthalmologist before this drug? I am not sure.

DR. AFSHARI: For me, thinking back, I am okay if

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

126

the patient has HSV to give them Lumigan, and I am okay if they have had corneal transplant to give them Lumigan. If they have persistent SPK or anything like that, then an ophthalmologist is following them and would be the one who would be prescribing this medicine and the patient already knows that they have some other problems. So, confounding. So, that is a different story. So, I guess I am okay with corneal transplant as well.

DR. MILLER: Am I allowed to speak?

DR. REPKA: Yes, please.

DR. MILLER: Do we have to try to help decide what side effect--the patient notices redness; the patient notices burning. I mean, what sends them to the ophthalmologist? Certain side effects would send you to the ophthalmologist. I don't know if they have to see an ophthalmologist beforehand.

DR. REPKA: I have one. What standard would the agency apply to the reuse of the non-reusable applicators, analogous to what your friends on the devices side deal with for contact lenses all the time? You know, the tendency of the patient to continue to use a previous device for economic reasons.

PAPER MILL REPORTING  
(301) 495-5831

128

just asking.

DR. CHAMBERS: Wiley Chambers. I don't know the answer. Dr. Whitcup?

DR. WHITCUP: Dr. Chambers, standards for sterilization are pretty high. Probably the only way to do that is by providing the sterile single-use applicators. It is something we can look into down the line. It is really a great thought given your concerns.

But then how do you check that, you know, the patients are sterilizing them properly, given potential risk? You know, we have gone through a fair bit of rigor to produce these brushes and applicators and make sure they are sterile. That is probably the best way to ensure it.

DR. REPKA: Dr. Afshari?

DR. AFSHARI: I am thinking that the single-use applicator can be something like what we have for Restasis, the little bottle for the preservative-free artificial tears. The patient can just close their eyes and put it on. Is there a reason that there has to be a specific applicator Because they can close their eye and just apply it.

DR. WHITCUP: We have thought about a number of

PAPER MILL REPORTING  
(301) 495-5831

127

DR. CHAMBERS: Wiley Chambers. The requirement for ophthalmic drugs is that all the products have to be sterile. That is, any container or applicator that is packaged with the drug product is considered a drug even though it is a physical apparatus. So, they all fall within the condition. So, the instructions will be to use it once and then dispose of it. Those are the same instructions that say try not to touch your eye with the applicator. We can put those statements in the labeling. To the extent that people are actually going to do it or not we have limited control.

DR. REPKA: Though the manufacturer might have control by being certain that they have provided an abundance of applicators per volume of drug.

DR. CHAMBERS: And, clearly, we would ensure that there were enough for what was expected to be the duration of the product. Otherwise, absolutely, you are setting yourself up to expect to have a problem.

DR. REPKA: Dr. Miller?

DR. MILLER: In this era of recycling and waste minimizing, is there a way within the requirement to sterilize the applicator at home or clean it somehow? I am

PAPER MILL REPORTING  
(301) 495-5831

129

packaging configurations and, clearly, down the line we may work with FDA to see if there is something that actually is easier for patients or better for patient safety. Initially, because we have the best experience with Lumigan in the bottle that it comes in, in terms of sterility and stability, we felt that that was the best way to at least get the product out. We can look at other configurations like single-use vials as well.

If you talk about waste, then you have these single-use vials that you are throwing out. So, it is a balance and I think down the line we will be looking at a number of ways as we get patient feedback, to improve over time.

DR. REPKA: Thank you, Dr. Whitcup. Other comments or suggestions? Miss Cofer?

MS. COFER: I have sort of a follow-up to Dr. Majumder's comment about the temporary effect of the drug. I don't know if FDA has considered, in the labeling, to state in the indications that it is for temporary increase of eyelash growth.

DR. REPKA: Thank you. As I see no other commentsB-Dr. Chambers, you may have some comments to make

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

130

before we close or anyone else from FDA.

DR. CHAMBERS: I guess I think I have only heard from Dr. Miller about pediatrics. Are we in agreement? Actually, I did hear from a couple of people. Are we in agreement that no age restriction would be placed? Is that the consensus of the group, but that you would like it studied in diseases which cause loss of eyelashes in the pediatric population? Is that what I am hearing?

DR. REPKA: Dr. Miller?

DR. MILLER: Conceptually, the loss of lashes with chemo or perhaps autoimmune disease could be studied in adults but including pediatrics in the group, and somehow a way to monitor it if you, as a physician, wanted to use it in a younger group.

I am afraid if you say you cannot use it less than age 25, then I would have to wait six years to consider using it in a pediatric case. Is that true? I mean, if you say not for use less than age 18? Explain to me what happens if you say you cannot use it in the label.

DR. CHAMBERS: If we say you cannot use it in the label then, one, there has to be a reason why we are saying that. Two, from the pediatric plan perspective, we have to

PAPER MILL REPORTING  
(301) 495-5831

132

data, the lash data nor the iris color change data that is as robust as I think any of us would like, and I would certainly like to see a better study of that population who will probably use it for a longer period of time and more frequently than the older populations. Dr. Afshari?

DR. AFSHARI: Is it possible to put something in the label that it is to be used in the pediatric group with extreme caution? Or, how could that be worded, something like that?

DR. CHAMBERS: It is obviously possible to put it, but the question is, is there a scientific basis to do it? Is this just because we are being paternal and protective or maternal and protective, whichever phrase you want to use? Or, do we have a scientific reason to do it? Or, are we just personally uncomfortable because it is cosmetic and shouldn't be there?

DR. REPKA: Well, I think my scientific basis was that we don't have the data in that population. Frankly, even in the BEG 032 there were very few patients that were that young or even close to that age group, and certainly all the Lumigan data is largely older. So, we have no racial data to speak of in the younger patients.

PAPER MILL REPORTING  
(301) 495-5831

131

either be studying it there or we have to say there is a safety reason not to and we have to identify what that safety reason is if we are not going to study it.

If you ultimately use it, if it does say that you can't use it in a particular age, you would then be using it off-label and you would have various reimbursement issues that are associated with it and you would have potential malpractice issues that are associated with it. But you are still within the practice of medicine. You can choose that that is in the patient's best interest.

But, you know, our preferred method is to label it where it is appropriate. So, if it is appropriate we should be labeling it so and/or studying it if that is what it takes.

DR. MILLER: Right. So, I am not asking for an age requirement.

DR. REPKA: Wiley, in my earlier comments, actually I was a little uncomfortable with teenagers using this drug with the limited data we have. Certainly the vast amount of Lumigan experience is not in that population where we have the safety data.

We really don't have the skin hyperpigmentation

PAPER MILL REPORTING  
(301) 495-5831

133

DR. CHAMBERS: Right, but the answer to that then is okay until you study it?

DR. REPKA: I think you need to. Dr. Majumder?

DR. MAJUMDER: This is partly a question, but I would see a big difference between saying, you know, the manufacturer or sponsor did a trial looking at this age group so we are approving it for this age group versus saying, you know, you cannot use it in a younger population. I just remember in their materials I think they actually contemplated that the use in adolescents would be off-label.

In other words, it wouldn't be an approved use but we have no reason to believe it would be particularly unsafe in that group. We just don't have the data to support approval at this time. So, is there a difference between saying, you know, approved for this group versus, you know, don't use it in a different group? I guess that is the question.

DR. CHAMBERS: There is obviously a difference in the language, but the goal is to try and figure that out so we would then design the appropriate studies. We can defer pediatric studies if we think that is what is the appropriate course, and then ultimately include the results

PAPER MILL REPORTING  
(301) 495-5831

ProTEXT Transcript Condensing for Windows

SHEET 35 PAGE 134

134

of the trials when they are done.

We also take note, and I will let Dr. Wilson speak for himself, but as has been pointed out, there is a fair amount of data.

DR. REPKA: Dr. Wilson?

DR. WILSON: Just for clarification, I forgot, but the efficacy trial that was presented was 18 and over? Is that right?

DR. CHAMBERS: That is correct.

DR. REPKA: But if you look at the sub-stratified data most of those patients were way older than 18. Dr. Afshari?

DR. AFSHARI: I am thinking if we have no cautionary noteB-we have all the Lumigan data and it is all positive. On the other had, we don't have the data on all of the youngsters. But then if you are giving this to a five-year old and they have hyperemia and we need to examine these kids, that would mean almost an EUA. So, you know, at what age limit are we really okay to give this, given that they may have some hyperemia or something that we would really need to examine? And it is for the growth of eyelashes; it is not a necessity?

PAPER MILL REPORTING  
(301) 495-5831

PAGE 136

136

DR. CHAMBERS: Thank you very much for the comments and the time.

DR. REPKA: This meeting is adjourned.  
[Whereupon, at 3:00 p.m., the proceedings were adjourned]

PAPER MILL REPORTING  
(301) 495-5831

PAGE 135

135

DR. REPKA: Dr. Miller:

DR. MILLER: I mean, I can get a slit lamp exam on a five-year old, no problem, but I am a pediatric ophthalmologist. Potentially, you can make the statement that under age 18 they need to have seen an ophthalmologist, you know, potentially.

DR. AFSHARI: I am comfortable with that. Thank you.

DR. REPKA: Dr. Wilson?

DR. WILSON: I was just thinking about this and thinking about all the comments. I guess the way I would come down and look at this is that the study was done in 18 and over and I would feel most comfortable with that group. And, I guess I am with you, Dr. Repka, anything beyond that needs further study but it doesn't preclude them from using it as off-label.

I would think that for things like cancer and other kinds of situations like that, you know, a physician would take that into account and use it off-label if the indication so warranted. So, that is where my comfort level is, the way the study was done, 18 and over.

DR. REPKA: Thank you. Dr. Chambers?

PAPER MILL REPORTING  
(301) 495-5831