

# TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

OPHTHALMIC DEVICES PANEL  
NINETY-NINTH MEETING

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Pages 1 thru 154

Gaithersburg, Maryland  
May 11, 2000

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at

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

OPHTHALMIC DEVICES PANEL  
NINETY-NINTH MEETING

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Thursday, May 11, 2000

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620 Perry Parkway  
Gaithersburg, Maryland

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P R O C E E D I N G S**Call to Order**

DR. McCULLEY: I would like to call to order the Ninety-Ninth meeting of the Ophthalmic Devices Panel and turn the floor to Sara Thornton for introductory remarks.

**Introductory Remarks**

MS. THORNTON: Good morning and welcome to everyone here. I am very sorry for the delay. We have had some weather-related delays as well, so we were kind of waiting to see who actually could show up at the last minute.

This is the first day of the Ninety-Ninth meeting. There will be another panel session tomorrow as well. Before we proceed with today's agenda, I have a few short announcements. Please, everyone who is here, sign in regardless of whether you are panel, staff or guest and public and sponsor. We need all of your registrations.

Any of the handouts that are available for public distribution today are available outside on the registration table. Messages for the panel members and FDA participants, information or special needs should be directed through Ms. AnnMarie Williams, who is sitting over there by the door, or Ms. Carol Coy who is outside there in the registration area in general. The phone number for calls to the meeting area is 301-977-8900, if you need that.

In consideration of the panel, the sponsor and the agency, we ask that those of you in the audience and at the table with cell phones and pagers either turn them off or put them on vibration mode while you are in this room.

Lastly, will all participants speak into the microphone. Give your name clearly so that transcriber will have an accurate reading of your comments.

At this time, before I ask the panel to introduce themselves, I would like to extend a special welcome and introduce to the public who is joining us today, the panel, the FDA staff, a new panel consultant member who is with us for the first time today. That is Dr. Anne Louise Coleman who is here on my left.

Dr. Coleman is an Associate Professor of Ophthalmology and Director of the Center for Eye Epidemiology at the Jules Stein Eye Institute of the University of California at Los Angeles School of Medicine. She has published and lectured extensively and is internationally recognized for her expertise in the diagnosis and management of glaucoma.

I will now ask the other members of the panel to introduce themselves starting with Dr. Yaross.

DR. YAROSS: Marcia Yaross, Director of Worldwide Regulatory Affairs and Medical Compliance, Allergan, Irvine, California, and industry representative to the panel.

DR. JURKUS: Jan Jurkus, Professor of Optometry, Illinois College of Optometry.

DR. MAGUIRE: Leo Maguire, Mayo Clinic.

DR. McCULLEY: Jim McCulley, Professor and Chairman, Department of Ophthalmology, University of Texas, Southwestern Medical School in Dallas.

DR. BULLIMORE: Mark Bullimore, the Ohio State University College of Optometry.

DR. MATOBA: Alice Matoba, Associate Professor of Ophthalmology, Baylor College of Medicine.

DR. GRIMMETT: Michael Grimmett, Assistant Professor, Bascom Palmer Eye Institute, University of Miami School of Medicine.

DR. WEISS: Jayne Weiss, Professor of Ophthalmology at Kresge Eye Institute, Wayne State University, Detroit.

MS. THORNTON: At this time, I would like to let you know that Ms. Lynn Morris, who is our consumer representative to the panel, will be with us shortly. She has just arrived from the West Coast, due to one of those weather things. Drs. Jose Pulido and Joel Sugar will not be with us in the morning. They will be arriving probably around 1:00 or 1:30 this afternoon. But, they are on their way.

We, at the FDA, would like to extend our

appreciation to the panel for the time they have taken from their busy schedules to prepare for this meeting.

Speaking of meetings, we have cancelled the July panel meeting. At this time, I would like to turn it over to Dr. McCulley or, if you want, I can read the conflict of interest statement.

DR. McCULLEY: Why don't you.

#### **Conflict of Interest Statement**

MS. THORNTON: The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. The agency has no conflicts to report.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask, in

the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

#### **Appointment to Temporary Voting Status**

MS. THORNTON: I would now like to read the appointment to temporary voting status for today's session. Pursuant to the authority granted under the Medical Devices Advisory Committee charter dated October 27, 1990 and as amended August 18, 1999, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for this meeting on May 11 and 12, 2000: Dr. Anne Coleman, Dr. Michael Grimmett, Dr. Jayne Weiss and Dr. Leo Maguire.

For the record, these individual are special government employees and consultants to this panel or other panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. Signed, David W. Feigal, Jr., M.D., M.P.H., Director for the Center of Devices and Radiological Health, April 26, 2000.

Thank you, Dr. McCulley.

#### **Open Public Hearing**

DR. McCULLEY: I would like now to open the public hearing session of this meeting. Those who wish to come forward to the podium and speak are invited to do so.

Please identify yourself and any conflicts, what your interests are and economic affiliations or associations might be.

We have no one who has indicated they wish to speak beforehand, so the floor is open for those who wish to come forward and speak.

Seeing none, the open public hearing session of this committee meeting is closed.

We will now begin the open committee discussion with Division updates. Dr. Rosenthal.

#### **Division Updates**

DR. ROSENTHAL: Thank you, Dr. McCulley. I just wanted to inform the panel that, as of Monday, I am going on a detail to the Center Director's Office to work on issues relating to the Healthcare Financing Administration. It is four months, but it may be longer. We will see what happens. I plan to be back after my detail.

So Nancy Brogdon will be the Acting Division Director during my absence. Thank you.

DR. McCULLEY: You have no further comments, not that that wasn't a big one. That is enough.

#### **Branch Updates**

DR. McCULLEY: We will now turn to Branch updates. Jim Saviola, Chief, Vitreoretinal and Extraocular Device Branch.

DR. SAVIOLA: Good morning, everybody. There are two items I would like to update the panel on, both related to orthokeratology.

There has been another 51-OK cleared for the Paragon HDS-OK and Fluoroperm 60-OK, paflucocon B, Rigid Gas Permeable Daily Wear Contact Lens for Orthokeratology. It was cleared on April 17, 2000.

The lenses are indicated for use in the reduction of myopic refractive error in nondiseased eyes. The lenses are indicated for daily wear in an orthokeratology fitting program for the temporary reduction of up to 3.00 diopters of myopia in eyes with astigmatism up to 1.50 diopters. There is also a note in the indication to maintain the orthokeratology effect of myopia reduction, lens wear must be continued on a prescribed wearing schedule.

The only orthokeratology lens that has been cleared for marketing besides this Paragon lens is the Contex lens. It is remarkable to look at the similarities in outcome data for the two lenses.

In the Paragon study, 92 patients were enrolled with 57 completing a minimum of three-months wear. Of the potential 114 eyes, 113 showed some reduction of myopic refractive error. The average reduction was 1.7 diopters with a range of 0.125 to 4.50 diopters.

In the Contex study which was approved back in

1998, there were 69 patients enrolled, 55 completing three months. Of a total of 110 completed eyes, 106 showed some reduction in myopia with an average reduction of 1.69 diopters and the range of 0.25 to 4.25 diopters.

The specific outcome data from the Paragon study is part of summary of safety and effectiveness for the 510K. That is going to be available from the website once they post it.

The labeling information also describes the effectiveness limitations for this new lens. The average wear time required for patients was consistently about nine hours during the entire three-month study. For the Contex lens, it was about eight. There was variability in wearing time. At the end of the study, 35 percent of the subjects wore the lens eight to twelve hours while 26 percent wore the lens twelve to sixteen hours. Only 5 percent of the completed subjects wore the lens for less than four hours.

When the population of subjects that had the potential to achieve 20:20 uncorrected VA was considered-- that is, the eyes targeted for emmetropia--45 percent achieved 20:20 at three months. When all eyes, regardless of pretreatment BSCVA are considered, 80 percent were able to see 20:40 at three months.

This marketing clearance does not mean that FDA has approved the procedure of orthokeratology. It does mean

that the Paragon ortho-k lens design may be legally marketed for the intended use described in the product labeling. It is my understanding that Paragon intends to qualify their finishing labs to market this reverse-geometry design rather than allowing other authorized labs to cut the lens.

The second item is related to guidance for orthokeratology. The Guidance for Industry, Guidance for Premarket Submission of Orthokeratology Rigid Gas Permeable Contact Lenses, was issued by the office on April 10, 2000. This was released as a level-2 guidance document since it contained the same information that the division had provided interested manufacturers going back to the Contex clearance in 1998.

The shelf number for the document is 1134, and it is available from the CDRH Facts on Demand or the CDRH website. This document is intended to provide guidance to manufacturers who submit applications for RGP lenses intended for orthokeratology. A discussion of the clinical-testing issues for orthokeratology lenses was held at the February 12, 1998 panel meeting. This guidance document identifies specific clinical protocol recommendations and data-analysis tables to develop and evaluate safety and effectiveness data for these devices.

A large segment of the guidance document is devoted to a labeling template that includes the primary

package, a package insert, a practitioner fitting guide and a two-part patient booklet, Part 1, before the purchase of the device while they are considering it in Part 2 after they obtained it.

Detailed examples of specific labeling components required by regulation are provided. The primary goal of the labeling is to communicate reasonable expectations of success to the wearer.

The guidance for preclinical manufacturing, chemistry, toxicology and microbiology information should be addressed in an application are referenced to the existing Daily Wear Contact Lens Guidance.

Copies have been sent to current panel members, those in attendance at the February, '98 meeting, and to a few of the consultants with special interest in this area. It is a rather long document. It is about 70 pages, but only about seven pages of that relate to clinical-study design. About 50 pages are addressed for labeling and the remainder, the eight to ten pages, are for the data tables.

Since is a Level-2 guidance, comments may be submitted at any time and we are especially interested in receiving comments during the first 60 days that it is posted. The guidance will be revised based on review of substantive comments that we receive.

Thank you for attention. Do you have any

questions?

DR. McCULLEY: Does anyone have any questions for Dr. Saviola? Seeing none, Lawrence Romanell will now give us an update from the Microbiologist, Intraocular and Corneal Implants Branch.

MR. ROMANELL: Thank you and good morning, everyone. I wish to inform panel members of two events which have occurred since the last time that we met, the first one being on March 31, 2000, a reclassification notice for aqueous shunts and keratoprotheses was published in the Federal Register. These devices were reclassified as Class II devices and their reclassifications became effective as of May 1.

Secondly, within the past month, two of our branch's biomedical engineers, Mr. Don Calogero and Ms. Ashley Boulware, participated in ANSI and ISO standard meetings in Shanghai, China. These meetings were held to discuss new standards for refractive implants and multifocal intraocular lenses.

The ANSI organization has begun work on these standards and the ISO committee is currently voting on establishing these draft standards as new work items. The ISO committee membership seemed receptive to using the ANSI Draft Standards as starting points for their own standards.

Additionally addressed at the ISO meeting were

draft standards for ophthalmic irrigation solutions and endotamponades.

Thank you for your attention. I will entertain any questions at this time.

DR. McCULLEY: Questions? Dr. Rosenthal?

DR. ROSENTHAL: I'm sorry; I forgot to announce that, during Donna Lochner's absence, we have appointed two new acting branch chiefs. I should have done that in my Division Update, but I will do it in the ICIB Update. Jan Callaway will be the Acting Branch Chief for ICIB for the first three months, which I am not sure when it ends, but-- the end of July. And Karen Warburton for August, September and October.

So, for those of you who want to contact the new branch chiefs, Jan Callaway for the first three months and Karen Warburton for the second.

DR. McCULLEY: Mr. Romanell is--

DR. ROSENTHAL: Acting for Jan Callaway today because Jan is acting as her original team leader for the PMA. That is how we did it.

DR. McCULLEY: And how is on second? No; who is on first? Now, our flower guy who is wearing a columbine, he has already told me, today. That is a pretty flower. Morris Waxler, Chief Diagnostic and Surgical Devices Branch.

MR. WAXLER: I have just two items. One, I would

like to inform you that FDA approved P970043, Supplement 5, Autonomous Technologies laser for LASIK treatment for myopia with and without astigmatism on May 8 of 2000.

Also, the P990078, Sunrise's laser thermokeratoplasty laser remains under review. If you have any questions, I don't know what I would do with them.

DR. McCULLEY: Any questions or comments? I'm sorry; your first comment was--I know you said it, and it was clear. My mind wandered. What did you say the first item was?

DR. WAXLER: Autonomous Technologies laser for LASIK treatment of myopia with and without astigmatism was approved on May 8.

DR. McCULLEY: Myopia LASIK.

DR. WAXLER: Correct.

DR. McCULLEY: Okay. Thank you. Any questions or comments for Dr. Waxler? Thank you.

**PMA P930016/S010**

**VISX START EXCIMER LASER SYSTEM**

DR. McCULLEY: We will now begin deliberation on PMA P930016/S010. I was informed that I guess I should tell you that S010 means Supplement 10.

Now that we are all straight on that, we will begin with sponsor presentation. I would like to remind sponsor that you have, by the clock, one hour for your

presentation.

**Sponsor Presentation**

MR. PATINO: Good morning, distinguished members of the panel, FDA, ladies and gentlemen.

[Slide.]

I am Dave Patino, Vice President of Regulatory Affairs and Clinical Affairs at VISX, Incorporated. VISX is here today to present the results of our clinical trial for the VISX Star Excimer Laser System for the treatment of hyperopia with astigmatism.

[Slide.]

Presenting for us today, in order, are Kitty Legerton, Director of Clinical Affairs at VISX, Dr. Ken Greenberg, Medical Monitor for VISX, Dr. Richard Braunstein, Principal Investigator, Dr. Richard Chiacchierini, Statistical Consultant, and Dr. Marc Odrich, Medical Director for VISX.

[Slide.]

The VISX Star Excimer Laser System is used for the majority of laser procedures, certainly in the United States and worldwide. The VISX Excimer Laser System is approved by FDA for a broad range of refractive indications which include PRK for low to moderate myopia, approved in March of 1996, PRK for low to moderate myopia with astigmatism, approved in April of 1997, PRK for high myopia with

astigmatism approved in January of 1998, PRK for hyperopia approved in November, 1999 and LASIK for low to high myopia with astigmatism approved in November, 1999.

[Slide.]

The indication that we will be discussing today is for the treatment of less than or equal to 5.00 diopters of a hyperopic sphere and less than or equal to 4.00 diopters of astigmatism.

I should note that this is a PRK procedure. It is not a LASIK procedure. It is surface ablation. Evaluation by FDA and the advisory panel is based on valid scientific evidence as presented.

[Slide.]

Going to the study chronology slide, I will direct your attention to just a couple of these items. The first is the first treatment for this device or for this indication was performed in August, 1998. In June of 1999, a PMA supplement was submitted to FDA. In July of 1999, the FDA filed the supplemental application as an expedited review.

Thank you.

MS. LEGERTON: Good morning.

[Slide.]

My name is Kitty Legerton. I am Director of Clinical Affairs for VISX Incorporated. I would like to

review with you some of the details of the study that was used to generate the data for this presentation this morning.

[Slide.]

This was a multi-center unmasked non-randomized clinical trial for the treatment of hyperopia with astigmatism. Following the preoperative examination and surgery, patients were examined daily until reepithelialization was complete. Follow up then occurred at one, three, six and nine months following treatment. Fellow eyes were eligible for treatment after three months.

[Slide.]

A total of seven clinical sites contributed data to this trial across the United States from California to New York. A study team from VISX initiated each center individually and each center was monitored by phone and during periodic site visits throughout the course of the study.

[Slide.]

Enrollment varied by center and ranged from a low of 10 subjects to a high of 44 subjects over the various centers. A total of 172 patients were enrolled in this study and the data from 276 eyes will be presented here today.

[Slide.]

As you can see, the proportion of males and females in this trial is approximately equal. There was a mean age of 51 plus-or-minus 11 years with a range of 24 to 77. There were also approximately even numbers of right and left eyes. There was an overwhelming proportion of white subjects in this trial with a small number of other races also represented.

Approximately two-thirds of subjects wore no contact lenses before treatment and just less than one-third wore soft lenses while 10 percent wore rigid lenses just prior to treatment. I should also note that poolability statistics were performed and there were no statistically significant differences noted with regard to sex, race, primary eye or preoperative MRSE in the subjects enrolled in this study.

[Slide.]

Study accountability was excellent throughout and this slide represents the most current numbers presented to you in the most recent update. The number of nonavailable datapoints is represented by the orange bars at nine and twelve months and there was a very small proportion of eyes that were still not eligible for treatment at the twelve-month visit when the database was closed.

[Slide.]

Study equipment for this trial was standardized.

Everyone used a VectorVision CSV-1000 chart for logMAR visual acuity and contrast sensitivity. A Humphrey Atlas 990 topographer was used at every center. In addition, an Amoils' scrubber was used to remove the epithelium preoperatively and a non-contact specular microscope was used at five designated centers for specular microscopy.

[Slide.]

Follow-up examinations occurred periodically and included, of course, refraction and visual-acuity assessment as well as contract sensitivity for primary eyes.

Cycloplegic refraction and dilated fundus exam was performed preoperatively and at six and twelve months, post-op.

Specular microscopy was performed at five designated centers and patients were presented with a questionnaire preoperatively and at three, six and twelve months postoperatively.

DR. GREENBERG: Good morning.

[Slide.]

I am Dr. Ken Greenberg. I am the Medical Monitor at VISX, Incorporated. For the last five years, I have been a paid consultant to VISX, Incorporated. I am a lecturer in ophthalmology at Columbia University in New York City and am in practice in Danbury, Connecticut.

[Slide.]

This morning, I am going to present the safety

data for this clinical trial. I will discuss postoperative healing, both postoperative healing, both complications and adverse events, intraocular pressure changes as well as endothelial cell counts and, finally, best spectacle-corrected visual acuity.

[Slide.]

The hyperopic astigmatism PRK ablation profile extends out to 9 millimeters. As a result, an Amoils' endothelial brush is used to remove the corneal epithelium to a diameter slightly over 9 millimeters as is seen on the video, followed by the stromal ablation.

[Slide.]

Following treatment, 86.6 percent of the eyes reepithelialized by day 6. On the slide, we see that, by day 7, 95.3 percent of the eyes has reepithelialized and, by day 13, all eyes reepithelialized. The medical monitors reviewed the eyes that took longer than seven days to reepithelialized and we found that there were no clinically significant events that occurred in these eyes and no trends could be identified.

[Slide.]

If we look at uncorrected visual acuity on the day of reepithelialization, over 40 percent of eyes had an uncorrected visual acuity on the day they reepithelialized of 20/40 or better whereas only 8 percent of those eyes saw

that well preoperatively.

[Slide.]

Relatively small numbers of patients had moderate or severe symptoms of pain, tearing, photophobia or foreign-body sensation on the day of reepithelialization and we can also note that a substantial portion of patients experienced no or mild symptoms of pain, tearing, photophobia or foreign-body sensation on the day they reepithelialized.

[Slide.]

Moderate to severe pain postoperatively peaked at day 2 and rapidly diminished. It is also important to note that a substantial percentage of patients experienced no or mild pain postoperatively.

[Slide.]

I am now going to discuss the complications and adverse events that are reported in this clinical trial. Complications and adverse events are undesired, clinically significant, changes from baseline in the operative eye. The medical monitors reviewed all complications and adverse events and, in consultation with the principal investigators, reports were generated that included a brief description of the severity and frequency of these events, the treatment required as well as the resolution of the events.

[Slide.]

Complications are events that are anticipated, transient and non-sight-threatening. This table shows the complications that were reported in this clinical trial. In the slides that follow, I am going to describe each specific event.

[Slide.]

Corneal edema was reported in one eye at one week posttreatment. In this eye, reepithelialization occurred at day 3. The corneal edema that was observed at one week resolved six days following treatment and the best spectacle-corrected visual acuity was 20/25.

In an additional eye, a recurrent corneal erosion occurred at three months posttreatment. This eye initially reepithelialized at day 5 posttreatment without any reported difficulty. At three months, the recurrent erosion occurred and, with conservative medical treatment, the erosion resolved in one week leaving a best spectacle-corrected visual acuity of 20/16.

[Slide.]

There were three eyes in this trial where there was foreign-body sensation reported at three, nine and twelve months, respectively. All of these eyes saw 20/20 or better best spectacle-corrected visual acuity.

Finally, there were four eyes in which ghosting and double vision was reported. This occurred in two eyes

at the six-month time point but resolved spontaneously by the nine-month visit. In both of these eyes, the visual acuity was 20/16 in one eye and 20/32 plus 1 in the other eye.

Two additional eyes experienced ghosting and double vision at the nine-month post-op visit. This, again, resolved by the twelve-month visit with best spectacle-corrected visual acuity of 20/25 plus 2 and 20/20. The topography that is seen on the right is from one of the eyes that developed ghosting and double vision at the nine-month visit. This explains the cause of the ghosting and double vision that was experienced in that we see, in the upper part of the topography, the significant dropout of data reflecting an irregular corneal surface.

Upon resolution of this irregularity and improvement of the topography, the symptoms of ghosting and double vision were eliminated.

[Slide.]

Adverse events are events that are serious, sight-threatening and unanticipated. Three eyes in this trial developed corneal infiltrates in the postoperative period.

In all three eyes, the infiltrates were peripheral and did not involve the area of ablation. All infiltrates were cultured and one grew Staph epidermidis. In one eye, the onset of this infiltrate was noted at postoperative

day 1. After treatment with vancomycin and gentamicin, this resolved at postoperative day 8.

In an additional eye, the infiltrate was noted on postoperative day 2. After treatment with Ocuflax, it resolved at postoperative day 8. In the last eye, the onset of the infiltrate was postoperative day 4. It resolved on postoperative day 11 after treatment with Tobradex.

The best spectacle-corrected visual acuity in these three eyes was 26/16, 20/25 plus 2, and 20/20 respectively.

[Slide.]

All subjects in this trial were put on a standardized steroid regime postoperatively. At the one-month time point, subjects were using fluoromethalone, 0.1 percent, QID. In seven eyes, an increase in intraocular pressure of 6 to 10 millimeters of mercury above baseline was noted. At the three-month visit, subjects were using fluoromethalone, 0.1 percent, BID.

At three months, six eyes were noted to have an increase intraocular pressure of between 6 and 10 millimeters of mercury above baseline.

[Slide.]

Endothelial-cell studies were done at five selected sites. There were no statistically significant changes in endothelial-cell studies at any point

postoperatively.

[Slide.]

The remaining slide will address best spectacle-corrected visual acuity. This slide shows loss of best spectacle-corrected visual acuity over time and we have divided them into two groups, those that have a greater than or equal to a two-line loss of best spectacle-corrected visual acuity and those that have more than a two-line loss of best spectacle-corrected visual acuity.

I would like to point out that, at the three, six, nine and twelve-month time points, we exceed FDA guidance. In fact, at nine and twelve months, there were no eyes that lost more than two lines of best spectacle-corrected visual acuity.

There were, however, four eyes that had a two-line loss of best spectacle-corrected visual acuity and we will look at these eyes specifically in the next slide.

[Slide.]

At nine months postoperatively, three eyes were noted to have lost two lines of best spectacle-corrected visual acuity in the 2.00 to 3.00 diopter manifest refractive spherical equivalent group. In all three eyes, the loss of best spectacle-corrected visual acuity resolved at the twelve-month time point.

There was one eye at the twelve-month time point

that did have a loss of best spectacle-corrected visual acuity of two lines in the 7.00 to 8.00 diopter pre-op MRSE group. We see that this eye had a pre-op refraction of plus 5.75 plus 3, axis 90 degrees, yielding a visual acuity of 20/20 plus 1.

At the twelve-month visit, the patient came in with a refraction of plus 1.75 plus a 0.75 axis 90 degrees with a best spectacle-corrected visual acuity of 20/30 2 plus 1, a two-line loss.

After discussions with the principal investigator, it was noted that this patient had started taking Serazone or nafazalone, which is an antidepressant. The most common side effect of this antidepressant is blurred vision, according to the PDR.

This patient was then asked by the principal investigator to return two weeks following their twelve-month visit. At this time point, the patient had discontinued the use of this antidepressant medication. We can see here an improvement of visual acuity back to 20/20.

[Slide.]

This slide shows best spectacle-corrected visual acuity over time in eyes that were worse than 20/40. Again, we have broken them down into two groups; all eyes versus those eyes that had a pre-op best spectacle-corrected visual acuity of 20/20 or better. The inclusion criteria in this

study dictated that patients must have a best spectacle-corrected visual acuity of 20/20 or better preoperatively to be included.

Therefore, there were some patients in here that did not have a best spectacle-corrected visual acuity of 20/20 preoperatively. If we look at the three, six, nine and twelve-month time points, we exceed FDA guidance. In fact, there are no eyes that had a pre-op BSCVA of 20/20 or better that were worse than 20/40 at any time point from three months on.

DR. BRAUNSTEIN: Good morning.

[Slide.]

I am Dr. Richard Braunstein. I served as principal investigator at Columbia Presbyterian Medical Center for this clinical trial. I am an assistant professor of clinical ophthalmology at the Columbia University College of Physicians and Surgeons. I would also like to acknowledge that I am a paid consultant to VISX and have a few shares of VISX stock.

[Slide.]

I will be discussing the analysis of effectiveness for this clinical trial and I will discuss uncorrected visual acuity, predictability, reviewing the psychometric analysis and patient questionnaires, residual astigmatic error, the vector analysis that was performed and the

stability data.

[Slide.]

Looking at uncorrected visual acuity over time, we see that at six, nine and twelve months postoperatively, more than 49 percent of eyes saw 20/20 or better without correction and greater than 95 percent of eyes saw 20/40 or better without correction and six, nine and twelve months.

This exceeds the FDA guidance level of 85 percent, 20/40 or better. At the request of our FDA reviewers, we have broken down and stratified the uncorrected visual acuity data by pre-op MRSE.

Looking across the table, we can see that, for all of the groups at twelve months, the FDA guidance level was exceeded.

[Slide.]

Similarly, when we stratified by preoperative sphere, the uncorrected visual acuity for 20/40 or better, the FDA guidance level was exceeded for all groups at the nine- and twelve-month time period.

[Slide.]

I will now discuss intended versus achieved correction. Looking here at the manifest refracted spherical equivalent at three, six, nine and twelve months, the FDA guidance levels for plus-or-minus a 0.50 diopter and plus-or-minus 1.00 diopter were exceeded.

[Slide.]

This data was also stratified at the request of FDA reviewers. Here we are looking at intended versus achieved for plus-or-minus 0.50 stratified by pre-op MRSE. What we see is what we have seen in all previous clinical trials, that, at higher levels of attempted correction, there is a smaller percentage of eyes within plus-or-minus 0.50 diopter.

Please note that as we go to higher levels of attempted correction, the sample size is decreasing, making statistical analysis less valuable. To highlight that, we see the 6.00 to 7.00 diopter group which seems to have wonderful results yet represents a very small sample size.

We see the same pattern when we look at the intended versus achieved for plus-or-minus 1.00 diopter, again stratified the same way, the same pattern and the same results in the 6.00 to 7.00 group.

[Slide.]

Cylometric analysis was performed as part of this clinical trial. Patients were asked to rate nine different aspects of their vision using a questionnaire on a scale of 1 to 10 from poor to excellent. They were asked to evaluate their preoperative vision using their corrective vision and their postoperative vision using their uncorrected vision.

[Slide.]

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This illustration shows overall sharpness and clarity, consistency of vision and overall visual comfort. What you can glean from this is that, postoperatively, there are fewer responses for fair or poor and an increased number of responses for very good and excellent.

[Slide.]

We see the same pattern of responses when patients were asked regarding close work, reading in dim light and driving in daylight.

[Slide.]

Again, for driving at night, driving at night with glare, general vision in dim light, less responses for poor and fair and increased responses postoperatively for very good and excellent.

[Slide.]

This table is presented at the request of FDA review and it presents residual astigmatic error at nine months, which is the point of stability, stratified by axis shift. I call your attention to the data in the red box. If we sum the first three numbers, we can see, from this table, that 84.2 percent of eyes at nine months has less than 1.00 diopter of residual astigmatic error.

This is to be compared with 47.1 percent of eyes which, preoperatively, had 1.00 diopter or less of refractive astigmatism.

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[Slide.]

Would like to share the vector analysis results. This is in all eyes which were targeted for emmetropia, at nine months, again, the point of stability. It involves 215 eyes. This analysis was performed with the commercially available Vector Inspector software which was developed by Mr. Julian Stevens at Morefield's.

This software converts, or requires that the data be presented in minus-cylinder format for analysis. Therefore, if you look at the sphere values, you will see that they are significantly higher than our pre-op MRSEs were. For cylinder, you will note that they are in minus-cylinder format.

I call your attention to two numbers on the table. This is the surgically induced refractive change versus the intended refractive change. For sphere when it is treated as a vector quantity, 90 percent of intended correction is achieved and, for cylinder, the same; approximately 90 percent of intended correction is achieved when it is treated as a vector quantity.

[Slide.]

This slide shows our stability data for the mean of the differences in manifest refractive spherical equivalent and average keratometry. In green, we see the manifest refractive spherical equivalent and, in red, the

keratometry. Please note that there is an expected overcorrection as we have typically seen in all PRK trials which occurs at one month with the data approaching zero for both keratometry and spherical equivalent between six to nine and nine to twelve months.

Please note that these two, the keratometry and the spherical equivalent, mirror each other. I call your attention to these bracketed numbers of 96.3 percent and 97 percent. These represent the percentage of eyes that, between visits at six the nine months and nine to twelve months, had a less than 1.00 diopter of change in manifest refractive spherical equivalent and average keratometry.

DR. CHIACCHIERINI: Good morning, distinguished panel.

[Slide.]

I am Dick Chiacchierini. I am the statistical consultant to VISX. I am the Senior Vice President for Statistics at C.L. McIntosh. I am the former Director of the Division of Biometric Sciences at the Center for Devices and Radiological Health. My financial interest in the company consists of my fee-for-service consultant basis.

[Slide.]

I have been asked by the company to discuss two topics with you this morning. The first topic is the sample size that is used for supplemental applications with lasers.

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To put this into perspective, the basis for sample size for sample size for ophthalmic laser studies which usually run in the 200 to 300 eye range has been based on safety concerns, so initial applications and initial submissions to the agency generally see in the range of 300 to 400 eyes.

That sample size was chosen with a concern for persistent, sight-threatening, complications which the agency prefers to have less than 1 percent. In fact, in the October 1996 guidance document, there are calculations which have indicated that if you observe zero of these rare complications in 300 patients, the upper one-sided 95 percent exact confidence limit is 0.99 percent, thus assuring that you are less than 1 percent.

Now, in the following two tables, we will present data that have been submitted to FDA as part of PMA P930016, the original PMA and the following supplements.

[Slide.]

What we have done in this table is simply to summarize the persistent site-threatening AEs as they occur in the various studies across all of the studies. In fact, we have calculated the percentage across all the studies after this sum and calculated the lower and upper 95 percent confidence intervals.

Then we compared them to the FDA-recommended limit. Looking at corneal infiltrate, and corneal ulcer, we

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should note that there were not zero events occurring during the studies. There were corneal infiltrates, as we have seen earlier this morning. However, these have not been deemed to be persistent because they resolve and, by twelve months, there are none of these events across any of the studies.

So the estimate of the percentage of corneal ulcers is 0.0 percent with an upper confidence limit of 0.36 percent which falls well below the 1.0 percent in the recommended guidance.

[Slide.]

The same is true for uncontrolled IOP change from baseline greater than 10 millimeters of mercury.

[Slide.]

If we move to late-onset haze with greater-than-or-equal-to two lines lost of BSCVA, there were, across the studies, ten of these events out of 1,032 patients. The estimate of the percentage is 0.97 which, out of a thousand patients is less than 1 percent. However, we note that the upper confidence limit does, in fact, exceed 1 percent.

For loss of ten letters of BSCVA, I should note that some of the patients in this row are included in here. That is what the asterisk stands for. There were twenty-seven of these events out of 1,032 eyes. The estimate is 2.62 percent with an upper confidence limit of 3.27 percent

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which is lower, much lower, than the 5 percent in the recommended guidance document.

To complete the picture, we look at the retinal detachment and retinal vascular accident. Again, there were zero events. Zero is the percentage with an upper confidence limit of 0.36 percent, well below 1.0 percent.

[Slide.]

To summarize this, the sample size used in the supplement, when taken in the context of the extensive experience from other data in this PMA, is sufficient to address device safety. Furthermore, from the data that we have had presented to us today on effectiveness, the sample size is sufficient to evaluate effectiveness.

[Slide.]

To address the second issue, there is always a concern with these kinds of treatments to the eye with stability. Stability can be looked at in a number of ways, and we have chosen to look at it a little bit differently than has been observed in the past.

We can statistical model maintained correction over time. It is expected, as you could see from Dr. Braunstein's presentation, that there is an overcorrection with a diminution of that effect with some stabilization occurring later in time.

It is expected that this change is a nearly

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exponential function so that the drop-off is nearly exponential. So the model that we modeled here, the function that we modeled here, was a natural log of 1 plus the correction and we made that equal a straight line.

[Slide.]

If we model all of the data from one through twelve months, and we plot the model predicted values, and compare it to the observed value which is located here, we get this kind of a function. One can see, from this function, that there is a rather large underestimate of the actual correction at twelve months.

In fact, if we had the one-month point on here, there would also be an undercorrection at one month so that the curve would look something like this. It would overcorrect at the center and undercorrect at the ends.

What that implies is that the simple exponential that we used was somewhat inadequate to explain the purpose. To adjust for this, there are a number of things you can do. What we chose to do was to look at the points later in the curve and to delete the early healing process with the same function.

If we do that, one sees that the slope flattens and that the estimate to the actually observed point is much closer. If we do that again and remove the three-month point, we get to the six-month line which is this green line

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here. Again, we see the flattening and we see that we are nearly right on top of the twelve-month estimate for correction.

We can also do this one more time. We can take the nine- and twelve-month values, as indicated in this red box. The interesting phenomenon that occurs here, however, is that that line flattens dramatically and the slope is no longer statistically significantly different from zero.

[Slide.]

So that there is no evidence of regression beyond nine months is demonstrated by the lack of significant slope between nine and twelve months. Generally, a lack of significance doesn't tell you very much. However, this lack of significance is based on over 400 datapoints in the nine- and twelve-month period and, therefore, we think we can have confidence in that outcome.

DR. ODRICH: Good morning.

[Slide.]

I am Marc Odrich. I am the Medical Director for VISX. I am Director of Refractive Surgery at Columbia University. And I am also a paid consultant to VISX.

[Slide.]

We have presented to you today the results of our study and we have the proposed indication of treatment of up to 5.00 diopters of hyperopic sphere with up to 4.00

diopters of hyperopic astigmatism in a PRK treatment fashion.

[Slide.]

To summarize our safety, our losses of more than two lines, the recommended guidance document levels, is less than 5 percent and, at twelve months, we are zero.

[Slide.]

BSCVA worse than 20/40 with eyes that started off with 20/20 or better best-corrected acuity is less than 1 percent and we have no events at twelve months. AEs of any type at twelve months, less than 1 percent and we are at zero. However, in fairness, we have presented one eye that had a loss of two lines at twelve months which was after the AE table was tabulated. But we point out that that patient was on a medication that had the primary side effect of blurring of vision and, upon discontinuation, was able to return to the best-corrected acuity.

Recommended levels of total AE events are less than 5 percent and we are zero percent. So, looking at a summary of safety, we have absolutely no concerns from a safety perspective.

[Slide.]

Our summary of effectiveness; uncorrected acuity of 20/40 or better, recommended level, was greater-than-or-equal-to 85 percent and, at twelve months, we showed you

data of 98 percent. Within 0.50 diopter, the recommended level is greater-or-equal-to 50 percent. We were 61 percent within 0.50 diopter of intended. Within 1.00 diopter of intended is greater-than-or-equal-to 75. We were 77 percent at twelve months.

Stability; this stability that we present here is what was presented in Dr. Braunstein's slide. The visit-to-visit difference between nine and twelve months being 1.00 diopter at any visit which was the level in the guidance greater-than-or-equal-to 95 percent. We were 97 percent at twelve months.

[Slide.]

However, we recognize that there have been different definitions of stability and remind all here that this is a study that began in 1998, meaning it was written prior to 1998, and that there have been several definitions. We have met every single one of these definitions.

Lastly, we have a definition seen from Dr. Braunstein and Dr. Chiacchierini's presentation that, when you look at the slope of the line between nine and twelve months, there is no evidence of regression beyond that nine-month period. Additionally, this is based on 415 datapoints between the nine- and twelve-month mark.

[Slide.]

In conclusion, the VISX Excimer Laser System has

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exceeded all guidance-document recommendations for both safety and effectiveness for the treatment of hyperopia and astigmatism in the full range that was presented.

Thank you.

DR. McCULLEY: Does that conclude sponsor's presentation?

DR. ODRICH: It does.

**Panel Questions for the Sponsor**

DR. McCULLEY: At this point, we will open for panel questions of the sponsor. Panel? Questions? Ones you wish to have clarified, ones you wish to challenge?

DR. BULLIMORE: With reference to the stability data, Dr. Odrich presented a slide showing the percentage of stability being based on an N of 134, but Dr. Chiacchierini presented data which he said, I guess it was for the same time period, was based on over 400 datapoints.

Could you clarify the discrepancy there?

DR. ODRICH: Marc Odrich of VISX. We submitted a supplement with Dr. Chiacchierini's points and the datapoints were 415 between the two. I will get you the reference page. It is not the N of 134, Dr. Bullimore. It is what is in our supplement. So you are correct. That is why we broke them out separately to make sure we presented both the N of 134 and what was presented in our supplement.

DR. BULLIMORE: My other comment is, listening to

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Dr. Chiacchierini, I was reminded of the statement I heard in statistics once, and that is that a absence of proof is not a proof of absence.

I was interesting in your treatment of confidence intervals with reference to the safety data. You are clearly very familiar with those and they were very nicely presented. I was disappointed that we didn't see confidence intervals for some of your slopes on your lines.

You finished by saying that you can't exclude--or your confidence interval includes a slope of zero when you only consider nine- and twelve-month data. What is the upper limit of the confidence interval for the slope of that line?

DR. CHIACCHIERINI: That was not calculated and submitted to the agency, Dr. Bullimore. In fact, the actual slope was a  $-0.0083$ .

DR. BULLIMORE: But you don't have that data?

DR. CHIACCHIERINI: I don't have the confidence interval on the slope.

DR. McCULLEY: Are you done, Mark?

DR. BULLIMORE: For now.

DR. McCULLEY: You don't need anything further clarified at this point; okay.

DR. MAGUIRE: Dr. Chiacchierini, I was wondering if you refer to, in tab 8A, page 18--do you have that

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information?

DR. CHIACCHIERINI: Dr. Maguire, we are getting it.

DR. McCULLEY: While you are looking for that, I would like to ask the FDA if FDA statisticians had an opportunity to look at the mathematical modeling data and to assess it and to offer FDA opinion as to its applicability and its strength, I guess.

DR. ODRICH: Excuse me; while the FDA answers, could we have that reference again?

DR. MAGUIRE: It is in tab 8A, page 18.

DR. ODRICH: A8?

DR. MAGUIRE: A8, page 18.

DR. McCULLEY: So we can't have two things going on, or this is not the appropriate time for that to be addressed?

DR. ROSENTHAL: The answer to your question is yes.

DR. McCULLEY: I guess that is all I need at the moment.

DR. ROSENTHAL: But it is inappropriate to discuss it.

DR. McCULLEY: At this point, but we will discuss it.

DR. ROSENTHAL: If the panel wishes to discuss it,

we will discuss it during the FDA presentation.

DR. ODRICH: We now have that, Dr. Maguire.

DR. MAGUIRE: This is a table that made me wonder about stability over time. When I look at the bottom of that, the mean change in MRSE is 0.55 from one to three months, 0.45, three to six months, and then, as you would expect from what you are saying with your slope, that the mean goes down to close to zero. That is good thing.

The thing I have a problem with is going to be a recurring theme in this which is individual variation that can get lost in group data. When I look at the standard deviation in change in MRSE, it is 0.78 early on, which you would expect if there were wide differences in stability over time. 0.55 three to six months which, again, if you are still being unstable, you expect to see that.

But the thing I don't understand, and I don't understand how it fits in with the little slope chart you presented, was that that standard deviation remains relatively high. It is not that much different than what it is at three to six months at the six-to-nine and nine-to-twelve month intervals.

I was wondering if you could just clarify for me how one can observe this type of standard deviation if things are stabilized, or if this would suggest that, although most of the people are stabilized and doing well,

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you have a subset of people that continue to be unstable over time.

DR. ODRICH: I am going to start by answering that and then I am going to ask Dr. Chiacchierini to comment, too. What you have just brought up, we have looked at some of the outliers. There are some significant outliers that fluctuate towards the end of the study.

I also point out, in 1992, the Zadnik article that, as the panel I am sure is well aware, there are some established errors of refraction and refraction-based standards looking forward. One of the standards that she came up with, although it is in a myopic population, is that there was an approximate error of refraction of 0.375 diopters.

That doesn't play directly to the standard deviation but it lets you know what, in a normal refracting myopic eye, you might expect. We recognize two things about these eyes; they have had corneal refractive surgery and there are some outliers, a significant number, in that later cohort.

So I think what you are saying is the correct observation. We have looked at that. We could find no pattern, however, and that was something that we tried to bring out with some of those losses of best-corrected acuity but, obviously, if you have enough fluctuation or the

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surface is irregular enough, you will expect to find some wide swings.

What gave us comfort was exactly what Dr. Chiacchierini told us, was that, in fact, this slope is not any different. So we do think it is exactly what you just said at the end that is causing this and that is the basis for it.

DR. MAGUIRE: So people evaluating this information kind of have to deal with some cognitive dissonance here. There is a part about it is good and that the overall trend is that things are stabilizing. But, at a minimum, in labeling, the panel also has to be concerned about what you have described as significant outliers.

What we need to do is, at a minimum, make sure that we have a good description of those outliers for both the clinicians who are going to be using the technique and, also, for the patients that are considering it. I wonder if you could comment on how VISX--what VISX would think, or the sponsor would think, would be the most appropriate way of informing people about those outliers.

DR. ODRICH: To go back just a little bit. In hyperopia, we did look at some of the outliers. We looked for trends and things like that to report. The only thing we do come up with is the patients are of an older age group, 51 years, as opposed to the myopes. They are

slightly over than our myopic experience of 37 years to the 51 years with a larger epithelial defect.

That larger epithelial abrasion, as it heals in some patients, takes longer. We did not find, and Dr. Greenberg presented this, a trend in those who had difficulty with reepithelialization the way we did in hyperopia. We found certain medications indicated that there might be a problem, first of all, with contact-lens handling and, second of all, with time to reepithelialization.

But we do suggest that this variability being present needs to be handled in our labeling as the observation. We can't make a comment on the trend because we didn't find any significant factors that we could point to.

DR. MAGUIRE: So, if I understand right, the continued refractive instability you find in a subgroup of patients. You have some outliers.

DR. ODRICH: It is not the same subgroup. It is changing. The nine-month group was not the same as the twelve-month group.

DR. MAGUIRE: Okay. So if you look over the group as a whole in kind of a pattern that defies pattern, we see changes in refractive stability over time. So we can't give a physician or patients--I want to make sure I understand.

DR. ODRICH: I don't agree with the word "stability," if I may. What it is is manifest refractive spherical--to be very specific. Because I remind you that it was the fact that these patients continued to see very well. So I think we have to look at all the variables and say that we have this one anomaly with the deviation from intended, intended versus achieved, which we have found no trend for.

The clinician certainly needs to be aware of it but I remind everybody that the patients really had a similar experience from six months out. Better than 95 percent of them were 20/40 and there really were no losses of best-corrected acuity.

I can find nothing more to say about it than that, other than to inform the doctor that we do have this significant fluctuation and that it is not the same group of patients.

DR. MAGUIRE: So we have a fluctuation in measured refractive area in a subgroup.

DR. ODRICH: Hyperopic; yes.

DR. McCULLEY: Dr. Odrich, let Dr. Maguire finish his statements.

DR. MAGUIRE: So we have evidence of variation of refractive area in a subgroup and it varies from period to period, and it doesn't fit a pattern. How is that

information going to be dealt with in labeling, or how would you suggest it be dealt with. We are interested in your suggestions.

DR. McCULLEY: Now, you may.

DR. ODRICH: Thank you. I think we need to discuss that with the panel and with the agency. I don't have a simple answer for it. I would recommend we just present the data the way it is.

I do point out that, as we follow--the number you were pointing out of 0.15 for the N of 134 with the larger deviation, there is also a second effect which is that that N of 134 that we presented are the first patients through. There is a learned effect, both by the doctors doing the surgery, that when you begin to enlarge the N, I do point out to you, that we have a much smaller mean change as the rest of the cohort drags through.

In fact, that was submitted to you in data-line listing format so we are not able to present it to you in tabular format because that represents a new analysis.

DR. MAGUIRE: But does the standard deviation remain --

DR. ODRICH: It remains approximately the same; yes.

DR. MAGUIRE: So that would suggest that there is continued individual variation. And that fact has not

changed for a particular cohort.

DR. ODRICH: Correct.

DR. McCULLEY: Do you have a sense of what--it almost sounds like there is a small pool that floats. Does that float over the entire continuum or is that within a defined group? This comes back, again, to what Dr. Maguire was asking you to do which--you know, you have a lot of time to think about it--which is how would you put this potentially in a label to inform physician and patient about this risk.

Is that risk to the whole population? You can float in and out of that? Or is it to a subgroup of the population that is 50 percent, 10 percent, 50 percent? Do you have an answer for that?

DR. ODRICH: The answer is we looked at sex, we looked at age, we looked at a variables that you would anticipate, and we could find none. So if you are asking is it a floating group, yes; but I suggest the N is very small.

DR. McCULLEY: What is the N?

DR. ODRICH: At nine months and twelve months, I don't have it off the top of my head. I can get it for you. I don't know it off the top of my head.

DR. McCULLEY: Do you have a suggestion as to how physician and patient could be effectively advised about this phenomenon? It sounds like you have a phenomenon for

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which you don't have an explanation. Presumably, if it is floating the way it is, it is not stromal change. It is epithelial change, would be best guess.

Have you looked to try to determine whether it is epithelial or stromal? It almost has to be one of the two.

DR. ODRICH: The question, I believe, is did we look and see if it is epithelial or stromal. The answer is I am not sure how we would do that.

DR. McCULLEY: I could tell you how to do that.

DR. ODRICH: We looked at maps. We looked at everything that we could find, and we found nothing.

Excuse me, I have one other comment. It is nine out of 207 at the last visit, nine eyes, that have more than 1.00 diopter. So we are looking at nine eyes at the last visit.

DR. McCULLEY: Last visit meaning twelve months?

DR. ODRICH: Twelve months, between nine and twelve.

DR. McCULLEY: How many eyes at nine months?

DR. ODRICH: We will get that for you.

DR. McCULLEY: Dr. Maguire, do you want to continue?

DR. MAGUIRE: I would like to continue. Let me propose, or just put up a potential proposal, and that would be to have, in your labeling, the examples of the ones that

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are the outliers and show what they do. At least that would show the physician what is going on because, when I look through some of your line data, there are some people that were like a +150, +150 that, at one month, were, like, - 5.25. Obviously, these are big variations.

I think one potential suggestion that we could discuss, and I would be interested in industry feedback on this, is to have some panel member or the FDA staff or someone go through all the line data that you so nicely presented to us with your supplementary thing since our review and actually list people.

What that would do would deal with the issue of outliers so that people could understand. I don't know what your feedback is or how you feel about that but that seems like one thing that is clinically accessible and does deal with the data that you have generated.

DR. McCULLEY: Do you have a response to that?

DR. ODRICH: Yes. I was leading to the fact that, since we can't identify a trend and we have looked at that, that that is definitely one option which is what I meant by saying we would notify the clinician of this. Certainly giving them synopses of the nine eyes in labeling is one option to do it, but any other recommendation we certainly would listen to.

I don't have an easy answer for it.

DR. MAGUIRE: To me, the most useful thing was--I went through about the first 47 in the line data and I found seven of those that had issues about them that if, I had it as a clinician, I would wonder. I think if, at a minimum, you give the clinicians access to that kind of information so that they can understand what happens when people do deviate and then what happens over time, that would be useful.

DR. MATOBA: You have mentioned several parameters that you have looked at and you said none of them correlated. Did you look at magnitude of the preoperative refractive error?

DR. ODRICH: We did.

DR. McCULLEY: And there was no--

DR. ODRICH: I'm sorry; there was no trend that we could find. The cautionary language--I don't want to mis-speak. We are looking at nine eyes out of 207 points at between nine and twelve. Ms. Legerton just gave me that it is eleven eyes of 207 at six to nine, a very small number. So finding trends is hard.

DR. BULLIMORE: Eyes that did what?

DR. ODRICH: Eyes that changed more than 1.00 diopter, the outliers that we have identified. I'm sorry.

DR. WEISS: Dr. Matoba asked one of my two questions. The second question was you indicated that one

reason, perhaps, for the high standard deviation was just inaccuracy of refractions which would be found in any study. Did you find the same large standard deviation at nine and twelve months down the line from your recollection in your studies with myopic patients?

DR. McCULLEY: I have to call for a point of clarification here. We usually don't compare between PMAs. Is that acceptable?

DR. ROSENTHAL: I think it is acceptable in the general context of refractive--

DR. ODRICH: I don't recall the number offhand, but it gets to the difficulty of refracting the hyperopic that we have discussed with panel prior in our hyperopia, there is more wobble in the hyperopic refraction. There are some references we can supply for that generally.

I don't recall--actually, that is not true. I recall one data point for our moderate myopes and low myopes was 0.40 between two three-month points. That would be between nine months and twelve months when we looked at them. So what we are citing here is 0.44 as the standard deviation, and it was 0.40 for one point that I am recalling off the top of my head for myopes with the caveat that the hyperopes are a slightly different group to refract.

I will say no more.

DR. WEISS: The last question; cycloplegic

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refractions, when were they done or were they a part of this?

DR. ODRICH: They were. They were done preoperatively at six months and twelve months. If you have a question about them, we can give you that data. I believe it was significant.

DR. WEISS: In terms of standard deviations, if you compare the six to the twelve months, because one would view cycloplegic as the gold standard, did you compare the six and the twelve months with the cycloplegic refractions as far as what the standard deviation is?

DR. ODRICH: We will get that for you. I think we did compare it a while ago, but I don't recall it off the top of my head. But we can get that number for you very quickly.

DR. BULLIMORE: I am not a paid consultant to VISX, but Dr. Odrich is right, a lot of the data that you see in terms of the standard deviation of 0.4 between nine and twelve is consistent with the literature. I would be surprised it were any lower for any population that was measured in a clinical cohort study like this.

DR. McCULLEY: I'm sorry, Dr. Bullimore, I couldn't understand the last part of what you said.

DR. BULLIMORE: The standard deviations that Dr. Maguire was pointing out, the variation between visits on

refraction, Dr. Odrich is right; you would see that in any test-retest situation even in a population where the refractive error is stable. That is a totally reasonable standard deviation.

DR. GRIMMETT: I would like to have the sponsor turn to I think it is table 6B, page 17, of section A8. I will ask my question while they are doing that. Dr. Chiacchierini presented information that the slope of the lines approach zero and, therefore, regression became less significant as time went on.

I would like to reconcile or have the sponsor reconcile some data presented in table 6B regarding undercorrections greater than plus 1.00 diopter. As time goes on, the percent of undercorrections--that is, those moving more hyperopic than plus 1.00 seemingly keep increasing. At three months, it is around 5 percent undercorrected. At six months, it is 11 percent undercorrected greater than plus 1.00.

At nine months, it is 19 percent. Twelve months is 22 percent. I just want to reconcile that information with the slope data that was presented that indicates that the slope is zero.

DR. ODRICH: I will start and Dr. Chiacchierini can come in. Two things. The 400 datapoints of Dr. Chiacchierini's are not the same group. The are eyes--there

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are 134 of them there, but there are more datapoints. So it is a little difficult to compare the two.

But there are larger numbers the you are pointing out coming across. Part of that is the cohort effect because we did not have an opportunity to update this specific table with the full data-line listing you see. So that actually would change.

We are not able to give you a full reanalysis of the numbers. Dr. Chiacchierini did do that for his slope. So they are slightly disparate populations. Also, be aware that there are relatively small numbers represented here.

DR. McCULLEY: Just to clarify. You had more patients reach the time point for examination.

DR. ODRICH: Correct.

DR. McCULLEY: In the data of Dr. Chiacchierini than you had in the original data that we had.

DR. ODRICH: Yes.

DR. McCULLEY: That data was presented to the FDA, as well?

DR. ODRICH: That is correct.

DR. GRIMMETT: So, in summary, if I understood correctly, we don't have the percent undercorrections for the updated data.

DR. ODRICH: Correct.

DR. JURKUS: I have a question regarding the

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patient questionnaires. For that information, were the patients asked to rate their aided or unaided acuity? When I look at the questionnaires, it is not very clear.

DR. ODRICH: We asked the patients in the operative eye and were specific to the operative eye to rate their best-corrected acuity preoperatively and then their uncorrected acuity postoperatively. So they were to compare what they could see at best before versus what they are seeing without any correction at the time of the questionnaire.

I would like to answer Dr. Weiss' question. She had a deviation question.

DR. McCULLEY: Go right ahead.

DR. ODRICH: At six months, the cycloplegic standard deviation was 0.83 diopters and the deviation was 0.92. As I recall, Zadnik's article, again, in a non-comparative population because it is mostly myopic, she, too, found approximately 0.90 diopters for a cycloplegic refraction was the standard deviation.

So it does remain very similar.

DR. WEISS: At twelve months? Do we have that?

DR. ODRICH: At twelve months, it was 0.92. At six months, it was 0.83. That is the standard deviation on the mean cycloplegic refraction at those time periods.

DR. McCULLEY: I would like to ask Dr. Bullimore

to comment. I hope you were paying attention.

DR. BULLIMORE: I was.

DR. McCULLEY: To your interpretation of what their data is relative to what one would expect in a normal, unoperated population.

DR. BULLIMORE: Were I to round up a group of patients, measure them at nine months, measure them at twelve months and they had nothing done to them, no refractive procedure, I would expect the mean change to be zero. But I would expect the standard deviation to be somewhere between 0.25 and 0.50.

So, in terms of the variability, the sponsor is correct. It may be that it is lost in the sheer numbers, and I don't want to exclude possibility that there are some patients who fluctuated widely, but, overall, the standard deviation is what one might expect.

Now, there is a trend toward hyperopia that is there. It is significant. The sponsor's own data showed that the confidence interval does exclude zero diopters; that is, there is still a significant shift from nine to twelve. That is quite clearly stated in their original PMA.

When you do other manipulations of the data, you can make that disappear. But the data that is originally presented shows a clear hyperopic shift from nine to twelve months that is highly significant.

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DR. WEISS: I am somewhat concerned that standard deviation doubles when the patients cycloplege because if it is just the inaccuracy of the refraction, why should it increase. That seems to speak to the fact that the inaccuracy of the refraction is also increased by the fact that the patients can accommodate when they have a manifest refraction. Then, when they can no longer accommodate, you actually will find more of a fluctuation then you did initially.

Could you address that issue?

DR. LEGERTON: I am Dr. Jerry Legerton. I am a paid consultant to VISX. Possibly, Marc was getting ready to respond to this, but the coefficient of variation, that point at which you have 95 percent confidence that the difference didn't occur by chance, for cycloplegic refraction as studied and published by Zadnik and others, is about 0.90 diopters for cycloplegic refraction. It is about 0.63 diopters for manifest refraction.

DR. MAGUIRE: There are studies that show that, especially in the more elderly population with dilation, you get significant differences in spherical aberration and that kind of business as you from a 3.00 to a larger pupil. That plus variability in optical aberration in these treated eyes should account for that.

That is one of the problems is how can you tease

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out changes that are due to accommodation from ones that are due to other factors. The bottom line is this is impossible given the guidance that we have now.

One question; you said, talking about the outliers at nine and twelve months, that is was nine eyes out of how many?

DR. ODRICH: 207.

DR. MAGUIRE: 207. Let's talk in terms of patients, though. Is it nine patients out of X, what?

DR. ODRICH: I don't remember that offhand. We can go back and locate it. I believe there may have been, in one case, two eyes in one patient, but I would have to go back and check. As I recall, there were two eyes in one patient at twelve months and then that number is eleven eyes at six to nine months that experienced--the outliers at nine months would have been eleven eyes and those were eleven patients.

That is my recollection having looked at this not in the past three days, so my mind is a little fuzzy there.

DR. MAGUIRE: It is important for labeling because what we are interested in is knowing the individual patient experience. If we are talking about nine or eleven over 200, that is one thing. If we are talking in terms of eyes and it is nine or eleven over 120, or 130, then we are talking about a different subgroup. Obviously, the clinical

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significance goes up.

So I am hoping that would show up, at a minimum, in the labeling.

DR. McCULLEY: Are there other questions or comments for sponsor? Then sponsor is now excused. Thank you.

DR. ODRICH: Thank you.

DR. McCULLEY: Let's take a brief ten-minute break. Everyone look at your own individual watch and let's all try to be back ten minutes from whatever your time shows to proceed. Thank you

[Break.]

DR. McCULLEY: We are going to reconvene deliberation on PMA P930016, Supplement 10. Dr. Waxler, you have no--you are already turfing? Jan Callaway, then, as the PMA team leader, will now take control.

#### FDA Presentation

MS. CALLAWAY: On March 27, 1996, in their original PMA application P930016, VISX, Incorporated of Santa Clara, California received approval for its argon fluoride excimer laser. The device, the VISX Laser System Models B and STAR was intended for use in photorefractive keratectomy, or PRK, to correct low myopia up to -6.00 diopters.

On April 12, 1997, the laser was approved for

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expanded indication of PRK with astigmatism up to -4.00 diopters. On January 29, 1998, for PRK for high myopia up to -12.00 diopter sphere with up to -4.00 diopters of astigmatism.

On November 2, 1998, the VISX STAR S2 was approved for PRK treatments of naturally occurring hyperopia, sphere only, between +1.00 and +6.00 diopters. On November 19, 1999, for laser in situ keratomileusis, or LASIK, for myopia up to -14.0 diopters with or without astigmatism from -0.50 diopters to -5.00 diopters in P990010.

In Supplement 10, the sponsor is requesting approval to further expand the indication statement for PRK treatments of naturally occurring hyperopia between +0.50 and +5.00 diopter sphere with astigmatism between +0.50 and +4.00 diopters.

The FDA team responsible for Supplement 10 included Dr. Malvina Eydelman, Dr. Bruce Drum, Mr. Mel Seidman, Mr. Joseph Jorgans, Ms. Paula Silverberg, Ms. Pam Reynolds and myself.

Dr. Eydelman will now present the areas in which your input is being requested.

DR. EYDELMAN: Good morning, ladies and gentlemen.

[Slide.]

Today, I will only highlight some points for panel consideration and will not present a comprehensive review of

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the clinical studies in this PMA.

[Slide.]

VISX is requesting the U.S. Food and Drug Administration's approval of the STAR S2 Excimer Laser System for PRK treatments of hyperopia from 0.50 to 5.00 diopter sphere with cylinder from 0.50 to 4.00 diopters.

[Slide.]

My written review was based on the analysis of the original and all the amendments received by FDA as of March 27, 2000. On April 26, the sponsor has submitted another amendment with updated cohort information.

The number of eyes available for analysis at nine months increased to 254 and the number of eyes available at twelve months increased to 237. This amendment contained data-line listings for all eyes in the updated cohort. The analysis of the updated cohort, however, was limited to accountability and stratified summary of safety and efficacy outcomes.

My comments today will incorporate all data available to FDA at the present time.

[Slide.]

The first issue I would like to direct the panel's attention to is stability. The slide presents analysis of the consistent original cohort of 134 eyes. As you can see,

between six and nine months, 96.3 percent of eyes had a change in MRSE less-than-or-equal to 1.00 diopter with a mean difference of 0.14 diopters or 0.046 diopters per month.

Between nine and twelve months, the numbers do not change much in this analysis. The sponsor has not yet submitted to FDA stability analysis based on the updated cohort.

[Slide.]

Clinical use of VISX STAR for PRK treatment of hyperopic astigmatism was performed by Dr. Jackson at the University of Ottawas General Hospital. While these eyes were not part of the PMA cohort, at FDA's request, the sponsor submitted copies of Dr. Jackson's presentations and conclusions.

In the April 26 amendment, the sponsor submitted updated analysis of refractive stability of Dr. Jackson's patients. Of the 57 eyes treated, this hyperopia with astigmatism, 19 patients had visits through 24 months. Twelve of these eyes had pretreatment parameters that matched the sponsor's PMA cohort. Stability analysis of these twelve eyes are presented in this slide.

[Slide.]

Analysis of some of the key efficacy outcomes was somewhat reduced from nine to twelve months. This slide

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summarizes the percentages and the associated 95 percent confidence intervals of the relevant values for the original and updated cohorts.

In light of these marginal decreases, together with stability analysis, panel members will be asked if nine months is the appropriate stability endpoint for evaluate of safety and effectiveness.

[Slide.]

Now I would like to direct the panel's attention to predictability outcomes stratified according to preoperative MRSE. This slide shows that, at nine months, both original and updated cohorts exceeded recommended predictability guidance values for all dioptric strata before 4.00 diopters of MRSE.

Predictability for the 5.00 to 5.00 diopter group, however, seems to decrease and 6.00 to 6.99 diopter group appears to have improvement in predictability, but at a closer look, one can see that it consists of very few eyes, three in the original and four in the updated cohorts.

[Slide.]

Stratified predictability at twelve months for the updated cohort reveals a similar picture with decreased predictability for the 5.00 to 5.00 diopter group. In light of these data, panel members are asked to consider whether additional limitations, in terms of MRSE, need to be

included in the refractive range for indication.

[Slide.]

The April 26 amendment also contained updated tables of patient questionnaire responses. I wanted to assure the panel that final labeling will reflect the appropriate outcomes.

#### Panel Questions for FDA

[Slide.]

Now for the questions. Question 1; has adequate refractive stability been demonstrated by nine months? Do the safety and effectiveness outcomes stratified by diopter of preoperative MRSE support approval for the full range of the requested refractive indication of +0.50 to +5.00 diopters of sphere with +0.50 to 4.00 diopters of cylinder.

The final question, No. 3; are there any specific labeling recommendations?

Thank you for your attention. This concludes my very brief presentation.

DR. McCULLEY: Thank you for your very excellent and thorough written review and for your brief presentation.

Are there questions, comments for FDA? I had one before. I am not a mathematical modeler. I wonder if the FDA statisticians have had a chance to assess that and give us an opinion relative to the--I guess FDA's opinion about

the mathematical modeling.

DR. EYDELMAN: I just asked Dr. Drum to comment on that.

DR. DRUM: This is Bruce Drum. In general, the type of analysis that was done is valid. It is often the case that you have data that you want to characterize but they don't fit a standard regression analysis, so you would do some sort of transform to try to approximate linearization of the data.

In this case, I don't believe that that is a very helpful approach. What was done was to look at all the data and then to look at all the data minus the first time point, and then all the data minus the first two time points, and it ended up looking at last two time points.

I think that, just looking at the actual refractive corrections at those last two time points tells us what we want to know.

DR. McCULLEY: You say you do or do not believe looking at the last two.

DR. DRUM: Right. I don't believe the regression analysis added anything to our ability to interpret the stability point.

DR. McCULLEY: My conclusion from the modeling was that there was stability between the last two time points.

DR. DRUM: There is detail that I think has

escaped explicit recognition so far. The slope of that difference curve may go to zero. That does not mean, necessarily, that stability has been reached unless the values of the curve also asymptote to zero at that point because these are changes from time to time.

Those changes have to go to zero for stability to be reached. So that is the question that we need to address.

DR. McCULLEY: Can you address it?

DR. DRUM: I believe that the original cohort of 134 didn't give us confidence that stability had been reached because the differences were similar for six to nine and from nine to twelve. They were about 0.14 and 0.15 diopters.

The last amendment that we got did have some updated numbers which looks like the trend is down from about 0.2 at six to nine to 0.1 or less at nine to twelve. So that is helpful.

DR. McCULLEY: What is your conclusion from that, that it, indeed, does approach "stability" with the larger numbers?

DR. DRUM: Maybe we should let Mel talk.

DR. SEIDMAN: I am Mel Seidman, the statistician. As far as the model, the model, you know, using the logarithm, helps to stabilize the data. And it does appear

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to be appropriate, mathematically. As far as checking the datapoints, we have not been able to do that because we didn't have the 400 datapoints and I am still unclear about that at this point.

Mathematically, it was shown that they stabilize at the nine-month period as far as Dr. Chiacchierini's model. I had one other question--

DR. McCULLEY: Does it relate to this same thing because I have a question about that.

DR. SEIDMAN: I'm sorry.

DR. McCULLEY: From what you are saying, then, what our position would be--and I understand that mathematical modeling can be variably done by different people and there are different opinions and attitudes, but I understand, from what you just said, or my interpretation of what you just said, would be looking at what was presented--from what everyone said, both of you said--that it looks as though stability may have improved. You are not certain yet whether it is absolutely convincing or not, but your caveat is you have not had a chance to look independently at those time points to offer us your final opinion relative to that.

DR. SEIDMAN: That's correct.

DR. McCULLEY: Which is very unfortunate, at least from my confused position.

DR. DRUM: I just wanted to clarify one point

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about the last thing I said about the most recent amendment. What was included in the amendment was just the correction values of the updated cohort and there really was no stability analysis included of the type that we have been requesting and that we received in the previous amendment.

So we still need to get that stability analysis to be able to fully evaluate the updated cohort.

DR. GRIMMETT: Just a clarification. I am slightly confused. The updated cohort, according to the data that we got in the latest amendment dated April 26 in Malvina's had 237 eyes. Yet people are talking about 400 eyes in the data Dr. Chiacchierini processed.

Can you reconcile that for me?

DR. DRUM: I am confused about that, too.

DR. McCULLEY: I kept hearing 400 datapoints. I am not sure how that jives with patient eyes. That was never really completely clear. Sponsor will have an opportunity to clarify that. I think that has a lot of us confused.

Other questions, comments? You had something else you were going to say.

DR. SEIDMAN: I just had another comment. Earlier, when Dr. Chiacchierini gave confidence limits for the whole supplement. This is for a different indication and so I just don't think it is right to use that as your

upper confidence limits based on the increased sample size.  
That's all.

DR. MAGUIRE: Dr. Eydelman, I also would like to thank you very much for an incredibly detailed, very helpful review. I wish I had read more of it before I independently did my own. It would have saved me a lot of time. But, I am a rookie, so I we are learning.

Could you comment on the methodology used to evaluate the efficacy of the cylinder correction and the stability of the cylinder correction? Do you feel comfortable with that?

DR. EYDELMAN: The sponsor has carried out the basic analysis that are usually required by FDA. So, in that respect, that is the usual analyses that are being asked of all sponsors.

DR. MAGUIRE: Okay. Thank you.

DR. McCULLEY: Other questions or comments? Does the FDA have any further response or direction to us at this point?

DR. EYDELMAN: No.

DR. McCULLEY: Then you may be excused from the table.

At this point, the agenda directs that we will allow fifteen minutes for additional comments from the sponsor, if you wish to.

**Additional Comments from the Sponsor.**

DR. CHIACCHIERINI: There were two points of clarification that we would like to make. The first involves the 400 datapoints. You accurately represented what was done. There were over 200 eyes at each of two points, the twelve-month and the nine-month, resulting in 415 datapoints in the cohort. That was the result of that.

With regard to combining the different indications, the assumption made on the AE combination was that the laser treatment, while for a slightly different indication, was, in fact, a shaping of the cornea done by the laser so that the exposures, and so forth, would be sufficiently similar such that we could combine those numbers. And we did this with some background from our clinical associates.

DR. ODRICH: I would also like to address this from a clinical perspective. That slide had lumped together all the PRK. We were very careful to keep no LASIK data in there as there may be other confounding variables.

But the device is the same device, whether it is used for myopia, myopic astigmatism, or hyperopia spherically or hyperopia with spherical astigmatism. So the fact that the device is the same should mean that our safety should be substantially similar. It is going through the same lens elements through the laser and the beam, itself,

is the same, seven beams rotating about the cornea.

So we felt, from a clinical perspective, this represented a continuum of the laser and its refractive capabilities and warranted our taking what has been submitted to the same PMA. These are supplements to the same PMA. Recognition of supplements is that it is the same device with different indications so that we are simply saying that it is, in fact, recognized as the same device because it is to the same PMA with different indications.

We, therefore, lump them and I think that clinically this is valid.

DR. McCULLEY: What you lumped was all hyperopic types of treatment?

DR. ODRICH: No, sir. We lumped myopia, myopia with astigmatism, high myopia. It is the same safety. We were speaking very specifically as a justification of sample size based on safety which is how we determine our sample size. It is always based on a safety endpoint.

DR. McCULLEY: Right; but the treatment profile is extremely different for myopia and for hyperopia.

DR. ODRICH: That is correct, but it is the same displacement to the beam, the same lenses. The same safety issues would occur regardless. And so, while you are absolutely correct, we are not saying that the efficacy or any of those variables are the same. We are suggesting that

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the device is effectively the same, to be considered in a very specific discussion of sample size.

DR. McCULLEY: Relative to adverse events.

DR. ODRICH: And complications. When you look at them, they are sufficiently similar. And we presented that as such.

DR. McCULLEY: Well, that might be arguable. I am not sure that it is in the context of our deliberations. I don't sense that there is anything that would raise major concerns with us about that. I think a point could be argued but I don't know that we have seen anything that would cause us great concern along those lines.

Does sponsor have any additional comments to make before being excused?

DR. CHIACCHIERINI: Just one small comment. The analyses that we referred to this morning was, in fact, in the April 26 submission to the agency. So, for what it is worth, it was part of that package.

DR. McCULLEY: Let's make sure that we are clear. The data that you used in your mathematical modeling was presented to the FDA on April 26.

DR. CHIACCHIERINI: Yes; in line-listing form. The actual analysis, itself, was also submitted on the same day.

DR. McCULLEY: But you presented the data. Your

point is you presented the data so that the analysis could have been done, time allowing?

DR. ODRICH: The analysis also was done.

DR. McCULLEY: Your analysis was done. As I understood it from the FDA, they did not have the data in sufficient time to repeat the analysis to confirm that they agreed with you. But you are saying that you did submit the data on April 26 and this is now May 11th, so relatively short.

I don't know how difficult it is to do the analysis with everybody's work load, but--

DR. ROSENTHAL: Let me just clarify this. The data that was submitted was submitted in data-line listing. Dr. Chiacchierini's analyses were submitted, but the other analyses, the ones of stability and whatever were not tabulated. So, yes; his was but the actual other ones that might support the company were not, so we couldn't--they could have submitted it, but they didn't, at that time. We are happy to take it, of course, post--

DR. McCULLEY: I am getting a little bit confused.

DR. ROSENTHAL: Do you want me to try to explain it again? Would you like Dr. Eydelman and Dr. Drum to clarify this completely?

DR. McCULLEY: Sally, is telling me we have to finish with them. But I am not sure but what, for the sake

of trying to get to truth here, fact as best we can--that we need to be too stylized in what we do. But maybe we do.

Let me ask if sponsor has any additional comments at this point.

DR. ODRICH: We have no further comments.

DR. McCULLEY: Thank you. You can be excused.

I would like to ask the FDA to please clarify, from their point, and what I intend to do and you can wrap me on the wrist later, is that, if this continues to be something that is not clear, that we will try to pursue it if it looks like it is important to pursue.

I think it is important for us in our deliberations until we kind of get to some reasonable comfort point. I don't want to beat it to death. I suspect that getting mathematical modelers together and to agree is, like we doctors are accused, it is like trying to herd a bunch of cats, that there is not always complete agreement as to an approach relative to an issue.

I could be wrong.

Dr. Eydelman?

DR. EYDELMAN: The April 26 amendment had data-line listings of all eyes in the updated cohort. It also contained Dr. Chiacchierini's analysis as presented today. It did not have stability analysis tabulated in the way we are used to looking at it; i.e., the way it was presented of

the original cohort.

That is what Dr. Drum was referring to in his comments, that we would like to see that kind of analysis before reaching a conclusion of how our opinion changes or does not change--

DR. McCULLEY: Relative to stability.

DR. EYDELMAN: Correct.

DR. McCULLEY: That is finally clear to me. Maybe I had to hear the same thing--

DR. ROSENTHAL: I thought I said the same thing, Dr. McCulley.

DR. McCULLEY: You probably did. I just probably had to hear it a second time.

DR. ROSENTHAL: It is just that Dr. Eydelman says is so much more clearly than I do.

DR. GRIMMETT: I would also, and this is probably an obvious comment and will get done when the data is tabulated but I would also like to see the FDA look at how the percent of undercorrections change with time additionally when the data is stratified by preoperative MRSE, and so on and so forth.

DR. McCULLEY: We will get to that later on.

We are at a point where it is almost 12 o'clock. We are ahead of our original schedule, but the next agenda item is committee deliberations. There can be break points

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in there, but I am not sure that we can be at a comfortable break point at a reasonable time. So I think, probably, it is best that we break for lunch now.

So, for one hour, again, look at your watches. Hopefully, we will do better this time. Let's reconvene one hour from now.

Let me remind the panel, please, a couple of things that we have been advised about in the past, and that is interactions with sponsors or industry that might be misinterpreted by others as demonstrating behavior that might be bothersome. The other is to remind you that we are not to discuss the PMA in any way amongst ourselves.

[Whereupon, at 12 o'clock p.m., the meeting was recessed, to be reconvened at 1 o'clock p.m.]

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

[1:00 p.m.]

DR. McCULLEY: I would like to call to order the afternoon session. We are deliberating PMA P930016, Supplement 10. We will start off with committee deliberations and the primary panel reviews. We will begin with Dr. Bullimore.

**Primary Panel Reviewers**

DR. BULLIMORE: Thank you, Mr. Chairman. Before I begin, I would like to apologize to the panel, the sponsor and the FDA for a small error in my review. My computer is equipped with the newest of operating systems and software and wherever I typed PRK, it changed it to LASIK.

DR. McCULLEY: It reads The Wall Street Journal.

DR. BULLIMORE: So I would like to apologize for that minor gaff.

I will keep my comments brief and try and focus my remarks on what I believe to be the stickier issues here. Accountability, very good. Safety, adequate. As far as efficacy is concerned, it is clear from the sponsor's presentation and the reviews that most of the target values in the FDA guidance document are reached or exceeded.

I would like to point out, however, that the degree of correction attempted in this cohort is modest in the majority of patients. The average spherical equivalent

attempted was the order of 2.50 diopters. So, when we consider efficacy outcomes, in particular the proportion of patients within a diopter of the intended correction, we have to bear in mind the modest change that is being applied.

My greatest concern as far as efficacy is the proportion of patients that are within a diopter. At ten months, that is the order of 76 percent and it appears to be declining. Extrapolating, we would expect that value to decrease further over time although the sponsor may have more data they want to share with us.

This probably reflects problems with stability as well as the predictability of the procedure. We have already had some discussion about stability. This has been a thorny issue in the past, issues related to hyperopia and LASIK correction, and this PMA is no exception.

The cohort regresses or shifts, depending on your perspective, in a hyperopic direction during the follow-up period. There may be some suggestion that the trend is slowing down, but, certainly, refractive error cannot be said to be stable by twelve months.

Between six and twelve months, there appears to be a linear change in the order of a third of a diopter. This may be explained in part by the change in keratometry values. What remains unclear is whether the small disparity

between refractive and corneal diopter changes are due to non-corneal changes--for example, the lens--or due to the limitations of the keratometry measure.

I should point out that cross-sectional studies suggest that subjects in their 50's, which is the mean age of this cohort, do shift, or appear to shift, in a hyperopic direction but it is only of the order of 0.05 to 0.10 diopters per year.

Although this is in the same direction as the patients in this cohort, the magnitude is considerably smaller. I propose the labeling include wording about the expectation of long-term hyperopic changes of up to half a diopter per year.

It is important to note the shift towards hyperopia is greater in higher corrections. The sponsor's own data, on page 70, attachment 5, shows data for patients undergoing corrections greater than 5 diopters.

For patients seen at nine and twelve months, the mean change is at least half a diopter in a plus direction. I think I overestimated that in my review and I apologize, again.

There is little evidence of stability in this subset and, as I requested in my original review, I would still like to see stability data stratified by attempted correction to see the extent to which these trends are born

out across the whole cohort.

I accept the analysis presented by the sponsor by Dr. Chiacchierini. I reject wholeheartedly and unreservedly the conclusions derived from that analysis. I don't think that the analysis shows stability. As I said before, the absence of proof is not the proof of absence.

When you are saying that the line cannot be distinguished from a slope of zero, one has to know the other end of the confidence interval as well. The data presented in the supplement is consistent with the data originally presented which shows a significant hyperopic shift between nine and twelve months in both sets of data.

The other thorny issue concerns the range of approval. The sponsor has requested for up to 5.00 diopter sphere with up to +4.00 diopters of cylinder. This would allow patients with up to 7.00 diopter spherical equivalent to be treated.

Only three of the patients-- I'm sorry; only three of the--that doesn't make sense. Who wrote this? Only three of the patients had 6.00 diopters or greater hyperopia and only 23 had greater than 5.00 diopters spherical equivalent.

As noted above, stability and efficacy appears to be, at best, marginal in the higher hyperopes and I am reluctant, therefore, to recommend approval about +5.00

diopters spherical equivalent.

I would like to reiterate that I would like to see stability data by refractive group. Astigmatism seems to be fine. I won't dwell on it although I have made some questions that the sponsor may choose or choose not to address.

I'm done.

DR. McCULLEY: Thank you.

Let's hold our questions for the primary reviewers until we have heard both.

Dr. Maguire, can you give us the highlights of your review and stress areas that you think you want to and think are important?

DR. MAGUIRE: I think Dr. Bullimore has concentrated on the accuracy and stability questions. I agree wholeheartedly with his analysis.

I think what I would like to do is, first, concentrate on what we talked about earlier today which are outliers, and identification of outliers. I apologize to sponsor in that, because I was at ARVO, I didn't get the line-item until Monday when I went to work. But I did work on the first 47 to the wee hours last night.

In that 47 people, there are some interesting observations. We have patients that are +4.00 +50 pre-op who are -1.00 +150, +50, +375 pre-op, still a cylinder at

twelve months post-op, +1.75 +3.75 pre-op, at one month post-op, -5.75 +1.00, remaining 3.75 +1.00 at twelve months post-op.

We have +3.25 +2.00 at six months, the last time data is available, -1.00 +3.50. We have +150 +150 pre-op, -5.00 +0.75 one month post-op, still at -3.75 +0.75. This is not in the monovision group. +4.00 +3.00 pre-op, at twelve months post-op, +2.25 +0.25.

So what we see is what sponsor spokesmen have discussed earlier that we do see outliers. We see some people who, with very low to moderate preoperative corrections that show severe myopic changes initially post-op and then go through variable degrees of regression.

We have some people that are fairly hyperopic pre-op with a lot of cylinder who can have all their cylinder corrected but only a portion of their sphere, and so on and so on. So one thing that I would certainly like to see happen is documentation of outliers that sponsor and panel can agree are clinically significant.

In the first 47, I think I have got seven or eight here that, to me, are clinically significant. Again, I would point out that these are seven eyes and, if we are talking about eyes, that gives us one denominator.

If we are talking about patients and what they have to go through, then that denominator is smaller. Seven

out of 47, that is a fairly good number.

The other thing to notice is that these don't occur just on the higher end of things, at least in this initial view of about maybe 20 percent of the dataset. It occurs in even very minor, relatively low, corrections. We need to have a better handle on that before we do final labeling.

So that is the first point.

The second point is, as has been said multiple times here today, epithelium appears to play a major role in wound healing. It is very difficult to understand how stromal changes, in and of themselves, could account for some of the big individual outlying fluctuations that we see in these patients.

So that affects stability, as Dr. Bullimore has concentrated on. I don't need to belabor that here. But it also impacts on patient expectations. Both the surgeon and the patient have to have an idea of what is going to occur in the postoperative period over the first three months, at least. The labeling has to be clear on that.

Let's start with the early postoperative period. Sponsors have noticed, in their safety and efficacy information, that a fairly large percentage of patients have mild or no pain in the initial postoperative period. It is true that those groups do exist.

But, in labeling and patient information, I think there should be a chart that gives a patient information in a way that they would be interested in seeing it. That would put pain on a Y axis, with severe pain at the top, moderate second and mild and none further down.

On the X axis, day 1, day 2, day 3 and day 4. If we look at it that way, we see severe pain. According to the protocol, these patients were all on pain medication as determined by the local physician. Severe pain is 9.1 on the first day, increases to 21.9 percent on the second, severe pain still in 11.2 on the third day. It is not until the fourth that it is down to below 1 percent.

Moderate pain, 18.8, day 1; 24.5, day 2; 21.2, day 3; and then, in day 4, back down again. So these are people that are going to go through a very uncomfortable process here for almost half a week in a very significant of patients, approaching a majority, of severe to moderate pain crescendoing at day 2, severe plus moderate to basically a little over 46 percent of patients, almost half.

That is significant and certainly should be in the labeling.

I think the epithelialization table that was given by sponsor in the most recent submission showing the table, that should be included in labeling. The early visual recovery, certainly. We are at 13.5 percent, still have

two-line vision loss, at least two-line vision loss, at one month post-op.

It is not clear why that goes. It is inferred that it is surface disease or punctate keratopathy. We need to have that labeled and we don't really know, in those patients, when they revert to normal between month 1 and month 3.

So labeling should certainly deal with that.

We have already talked about refractive regression.

Dr. Bullimore has alluded to accuracy and how patients within plus-or-minus 1.00 diopter of MSRE is reduced over time. Interestingly, uncorrected visual acuity remains relatively high even though we do see more people fading away from that plus-or-minus 1.00 diopter range. We really need some type of an explanation of that.

Finally, we have, besides subgroups based on refractive error that don't fall within FDA guidelines for at least plus-or-minus 1.00 and for plus-or-minus 5.00 for some of the outlying areas, we notice that five of the eight sites fall below FDA guidelines for MRSE within 1.00 diopter of target.

Contact-lens wearers pre-op fall below FDA guidelines for MRSE within 1.00 diopter of target. There are age and gender differences as well and these need to be

dealt with.

Miscellaneous concerns; we need labeling regarding retreatments and the fact that there is no knowledge of how effective they will be. The pupil-measuring device used in this system was not functioning properly so we have absolutely no information on a very important clinical issue which is the effect of pupil size on outcome.

We don't have any information on the incidence of spectacle wear after surgery for either distance and near. That is something that is fairly common on most and would be of interest to both the patient and the practitioner and, as in a lot of the studies, we have to have labeling considerations regarding race.

The last issue has do to with monovision. Many of the second eyes in this protocol could have monovision, but I don't think I see anywhere in the analysis here anything about the efficacy of monovision. Giving some of the variations and refractive accuracy here, I think that is something that needs to be looked into in detail before we can know, through labeling, whether monovision should be recommended or not.

That is particularly important when we see, in people who are going for just standard correction, that there is a significant drop-off in accuracy and stability of MRSE plus-or-minus 1.00 and plus-or-minus 50.00 as one goes

to larger corrections.

That concludes my comments.

DR. McCULLEY: I thank both of you.

DR. ROSENTHAL: Could I just make one comment about monovision. I think that if the company wants to include in their indications monovision, many of those issues that you talk about have to be addressed. If the company does not want to include it in their indications for use, then it is the practice of medicine and the issues have to be addressed in the labeling so that the physician can interpret them for monovision.

DR. McCULLEY: Basically, we have not had data presented to us relative to monovision. So we could not recommend approval for that in the labeling.

DR. ROSENTHAL: That's correct.

Did I make myself clear, Dr. Maguire?

DR. MAGUIRE: Yes, sir; you made yourself clear in that the FDA is not making any recommendations pro or con for monovision, and yet it is a part of the protocol here and should show up in the labeling with a warning.

DR. ROSENTHAL: That is fair enough.

DR. MAGUIRE: Is it reasonable, or is it legal, or whatever--is it reasonable to expect sponsor to include in their labeling and outcome data things that were part of their protocol such as monovision? To me, it makes it a

little bit more difficult to evaluate the accuracy and stability data when a lot of our people are not aimed at emmetropia, and yet we can't discuss monovision.

Maybe it is just one of dilemmas we have to live with.

DR. ROSENTHAL: It is a dilemma that, if it is not in the indication, the labeling, theoretically, does not have to address it directly. But all the issues relating to it should be spelled out so that if the doctor chooses to treat the patient for monovision, he or she has the information that allows them to do so.

DR. McCULLEY: I would think if sponsor isn't requesting it in the labeling that that, of course, can't be in the labeling. But since they did allow it in their protocol, having cracked that door, my personal response would be to say there needs to be a warning in the labeling that efficacy of monovision has not been shown with this procedure, rather than just leaving it alone, saying that it has not been shown.

DR. ROSENTHAL: I would like Dr. Eydelman to address this issue.

DR. EYDELMAN: In the PMA, sponsor has included the eyes for monovision in all the analysis except for UCVA. For the UCVA, they have stratified accordingly to the eyes that were aimed for emmetropia versus those that were not.

That is the standard way we have dealt with monovision eyes in every PMA for refractive laser that has come before the panel.

DR. McCULLEY: Is sponsor requesting approval for that?

DR. EYDELMAN: No; they are not.

DR. McCULLEY: Questions, comments for primary reviewers? There is remarkable concurrence and I think the discussions this morning probably dealt with a lot of our issues.

Does no one have any comment? I forgot to assign a scribe so I scribed. One point that I think we do need to discuss that I sensed we had not really dealt with and that is the range of approval.

I think the other issues we had pretty much discussed this morning. But the range of approval, we have not. So I think we need to put that on the table. Dr. Bullimore has a recommendation that the upper limit of approval be 5.00 diopters spherical equivalent. You would have to have something in there that related to upper limit of sphere, cylinder, potentially as well.

I think they have requested up to 5.00 diopters of sphere and 4.00 diopters of cylinder. So is there then an upper limit taking those two requests at their face value of a combined spherical equivalent being no greater than 5.00?

Is that the opinion of the panel or just Dr. Bullimore? If others have opinions, we need to hear them.

DR. MATOBA: I agree with Dr. Bullimore. But the problem is that their data is broken up by spherical equivalence. So they give us data 6.00 to 7.00 and 5.00 to 6.00, and those are the two groups that we are concerned about. But we don't know how those break down in terms of how much of the is from sphere and how much of that is refractive error from the astigmatism.

That might help us with our decision or our discussion if we had that breakdown.

DR. McCULLEY: The majority is going to have to be sphere. Is there any cross-cylinder or mixed astigmatism in this group?

DR. BULLIMORE: No.

DR. MATOBA: So it is all--

DR. McCULLEY: So plano +4.00 would be the spherical equivalent of 2.00.

DR. MATOBA: But you could have up to 4.00 diopters of astigmatism.

DR. McCULLEY: They did present their astigmatism data separately, I believe though, did they not?

DR. GRIMMETT: I agree with Dr. Bullimore's that if up to +5.00 sphere and +4.00 cylinder would allow +7.00 manifest refractive spherical equivalent, looking at the

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updated data submitted on April 26, table 1B, tab 4, the group from 6.00 to 6.99 manifest refractive spherical equivalent only has, what, four eyes.

So, I certainly agree that, at a minimum, based on this data, there is not enough to approve over 6.00.

With regards to approval over 5.00, while the safety is adequate, the efficacy falls off MRSE plus-or-minus a half and plus-or-minus 1.00, falling below FDA guidelines. Since there is no safety issue, that could be dealt with in one of two ways, either, as Dr. Bullimore suggests, capping the top end at 4.00, since we know that most refractive procedures have decreased efficacy at the upper end, dealing with it in the labeling and emphasizing that fact that it falls off at the upper end, still realizing that most patients starting out with a high MRSE will get a decrease in their hyperopia and will be benefitted in that regard.

So I think those are the two ways to deal with it. I think, at least from my perspective, based on this data, there is a paucity of data over 6.00 and I would, at a minimum, cap it at that.

DR. McCULLEY: So the difference here to resolve, relative to Dr. Bullimore's suggestion and yours, is 5.00 or 6.00, maximum spherical equivalent.

DR. GRIMMETT: Maximum spherical equivalent. And

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I would just like to hear other opinions in that regard regarding that subgroup. Perhaps Dr. Maguire would have a comment.

DR. McCULLEY: We need to come to a resolution on that. Dr. Maguire, would you like to comment?

DR. MAGUIRE: Let's say you went standard letter of the law by FDA guidance and used, as your resource, the most recent submission from sponsor. For MRSE, 4.00 to 4.00 at nine months post-op, 43 percent are plus-or-minus 50.00. That is below guidance.

That same measure for 4.00 to 4.00 at twelve months is 53.00. But, because the N is low, a lot of that 90 percent confidence interval is a lot below 53.00. For the 5.00 to 5.99, Dr. Bullimore has been talking about, before MRSE is 28.6 percent at nine months and 41 percent at twelve months. Both of those are below guidance.

DR. McCULLEY: In what category.

DR. MAGUIRE: For plus-or-minus 0.50. It should be 50 percent. They are 28 at nine and 41 at twelve months. Correct me if I am wrong.

If we look at MRSE plus-or-minus 1.00 for the 4.00 to 4.99 group at nine months, 75 percent are in that group and that is good. That is at guidance; correct? That is at the bare cutoff of guidance. At twelve months, it is 70 percent. That is below guidance.

For 5.00 to 5.99 for MRSE plus-or-minus 1.00, it is 57 percent at nine months and 45 percent at twelve months. So those are both below guidance. Also, at twelve months, for MRSE 3.00 to 3.99, it is 71 percent. That is below guidance.

DR. McCULLEY: 71 percent for 1.00 diopter.

DR. MAGUIRE: For 1.00 diopter, so below guidance. So, basically, what you are seeing is you are kind of seeing this transition that has been discussed before. If you went by the letter of the law, then you make your cutoffs accordingly.

Or, an alternative thing that Dr. Rosenthal has discussed before is you can give indications for MRSE for the ones where it is at guidance at all levels but still have the laser set up so that it can do the higher levels. It is just not FDA-approved.

DR. McCULLEY: Let me clarify something real quick.

DR. ROSENTHAL: No; let me clarify. I think I will clarify first. Generally, we do not go by each strata, each dioptric strata, and look at each one to meet guidance. In general, you take the bulk of them. It is when there are significant fall-offs that I think it is fair enough to make the cutoff.

So one expects, at the higher levels, to not

possibly reach exact guidance. So it is a gestalt more than it is an exact science.

DR. MAGUIRE: I recognize that.

DR. McCULLEY: And guidance is guidance, not policy. So it is not letter of law.

DR. ROSENTHAL: Right.

DR. McCULLEY: Having been here through all of this for years, we have refused to set guidance for high degrees of myopia or for hyperopia because of absence of data. The guidance that you are referring to is low myopia.

We left it as it was, preferring to use our judgment in these areas not covered because we didn't have the data to be able to set a different guidance. So that is kind of a road map and it is not letter of the law.

When FDA asked us, at one point, to consider setting guidance for the higher levels of myopia at one point and for hyperopia at another, we respectfully declined saying we didn't have data to be able to do that and we would use our best judgment using the previous guidance for low myopia as a guide.

DR. MAGUIRE: Basically, this was just a brainstorming thing. Basically all I was doing was applying the same criteria that sponsor applied when they didn't include their higher end because it didn't meet guidance. So it is the same thing in principle.

DR. McCULLEY: That relates to what Dr. Rosenthal said. They saw a fall-off and felt that that was not appropriate to pursue.

DR. SUGAR: Those were basically the comments I wanted to make. I would favor being more inclusive rather than exclusive, going up to 6.00 diopters spherical equivalent because the patients have no higher incidence of adverse events or safety issues and they have a very high prevalence of 20/40 or better uncorrected visual acuity. These are hyperopes who can accommodate the difference.

But I think that we should be more inclusive, not restrictive, and use 6.00 diopters as their top end.

DR. McCULLEY: The reality of dealing with a patient who is a +6.00 or a +1.00 or 2.00, you have got a lot happier individual with a +1.00 or 2.00 than a +6.00.

DR. WEISS: I would concur with Dr. Sugar's comments. In the labeling information, you could just have the information and the different strata so the physician and the patient can be aware.

DR. McCULLEY: So the consensus seems to be, and we will deal with this in our motion, would be that the upper limit would be set at 6.00 diopters spherical equivalent and we will have a chance to vote on that.

I don't know if Dr. Bullimore has been convinced, but I sense that the majority are at 6.00 rather than 5.00.