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PUBLIC HEALTH SERVICE
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OPHTHALMIC DEVICES ADVISORY PANEL

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Volume II

Open Session

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Janice M. Jurkus, O.D.

Jose S. Pulido, M.D.

Joel Sugar, M.D.

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Marcia S. Yaross, Ph.D., Industry Representative

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Malvina B. Eydelman, M.D.

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P R O C E E D I N G S

DR. McCULLEY: I'd like to call the meeting to order and turn the mike over initially to Sally Thornton for introductory remarks.

MS. THORNTON: Good morning, and welcome to all attendees. Before we proceed with today's agenda, I have a few short announcements to make.

During the break this morning, you may purchase coffee, tea and pastries in the cafeteria. Water fountains are available in the corridors adjoining the conference room area, next to the restrooms, which are adjoining the water fountains.

Gloria Williams in the back has a list for transportation services following the close of the meeting at 5 today. Would you please see her if you need transportation services and sign up there? She is at the front door, but she will be back at the registration table.

Messages for the Panel members and FDA participants, information or special needs should be directed through Ms. Ann Marie Williams, who is also at the front door, or Gloria, who will be available, as I mentioned in the back.

Will all meeting participants today please speak into the microphone--loudly--so that the transcriber will

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have an accurate record of your comments.

At this time, I would like to extend a special welcome and introduce to the public and Panel and FDA three Panel participants who have recently joined the Panel. This is for those folks who are here today that were not here yesterday. We would like to introduce you to Dr. Janice Jurkus, a Panel consultant and Associate Professor of Optometry at the Illinois College of Optometry in Chicago; Ms. Lynn Morris, our consumer representative, who is Communications Coordinator and Magazine Editor for Alumni Relations at the University of California, San Francisco; and Dr. Marcia Yaross, the industry representative, who is a full-time employee of Allergan in Irvine, California, a health care company, and has the position of Director, Worldwide Regulatory Affairs and Medical Compliance.

Greetings to you, and will the remaining Panel members please introduce themselves, beginning with Dr. Bullimore?

DR. BULLIMORE: My name is Mark Bullimore, and I am an Assistant Professor at the Ohio State University College of Optometry.

DR. SUGAR: Joel Sugar, Professor, University of Illinois at Chicago.

DR. MACSAI: Marian Macsai, Professor of

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Ophthalmology, West Virginia University.

DR. PULIDO: Jose Pulido, Professor of
Ophthalmology, Medical College of Wisconsin.

DR. HIGGINBOTHAM: Eve Higginbotham, Professor and
Chair, Department of Ophthalmology, University of Maryland
Baltimore.

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

MS. THORNTON: I just have one note of correction
on the agenda. The speaker time allocation given the
printed agenda for the open public hearing session is 5
minutes for those who have reservations or who are
requesting time to speak now.

I'd like to continue with reading into the record
the Conflict of Interest Statement for this session of the
Open Public Hearing.

"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 and all financial interests
reported by the committee participants. The conflict of

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interest statutes prohibit Special Government Employees from participating in matters that could affect their or their employers' financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved, is in the best interest of the Government."

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Janice Jurkus and James McCulley. Drs. Jurkus and McCulley reported current or past involvement in the form of contracts and grants and speaking engagements with firms at issue. Since these involvements are unrelated to the specific matters before the Panel, the agency has determined that they may participate in the Panel's deliberations.

In the event that the discussions involve any other products or firms not already on the agenda for which the FDA participant has a financial interest, the participant should excuse himself 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

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comment upon.

This is the Appointment to Temporary Voting Status. "Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, as amended April 20th, 1995, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for the duration of this meeting on February 13, 1998: Drs. Joel Sugar, Jose Pulido and Janice Jurkus. For the record, those persons are Special Government Employees and are consultants to this Panel or consultants or voting members of another panel 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, D. Bruce Burlington, M.D., Director, Center for Devices and Radiological Health, February 4, 1998."

Thank you, Mr. Chairman.

DR. McCULLEY: Thank you.

We will now open the public hearing session. We have not been informed prior to the meeting of anyone wishing to speak. We do have time allotted for public hearing. If there are those who would like to come to the podium and identify themselves and make a comment, we would welcome that at this time.

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[Pause.]

DR. McCULLEY: Seeing none, the open public hearing is closed. We will now begin the open committee discussion and ask Dr. Waxler for a Branch update.

DR. WAXLER: Good morning on Valentine eve.

I want to give special thanks to the Branch and introduce them, and I would ask Dave Whipple [ph] if we would give them each a flower--those who are here.

Everett Beirs [ph], who is a biomedical engineer and toxicologist; Bruce Drum, who is a physicist; Jan Callaway, who is a microbiologist; Quin Hong [ph], who is a biomedical and electrical engineer; Daryl Kaufman, who is a biologist; Denis McCarthy, who is a physicist; and Marsha Nicholas, who is a biologist.

In addition, of course, special thanks to Malvina Eydelman, our ophthalmologist, Medical Officer, and Bernie Laprie [ph], our optometrist, who do yeowoman and yeoman work.

In addition, I'd like to give special thanks to other members of the division who pitched in considerably, thanks to their Branch chiefs: Keesha Alexander [ph], who is a chemist; Ashley Bolar [ph], who is a biomedical engineer; Deborah Falls [ph], who is a biologist; Eleanor Felton, a biologist; Susanna Jones [ph], a toxicologist; and

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Karen Warburton [ph], a microbiologist.

Thanks, Donna Lockner [ph], and Jim Saviola [ph], for all of your help and support, and to Ralph Rosenthal and Nancy Brogdon as well.

It is quite a team effort, as you will see when I do the workload summary. Also, thanks to the statistics group at the agency in the Office of Compliance for their tremendous support, and staff in the Office of Science and Technology, and the Office of Health and Industry Programs.

Thanks to everyone.

On January 29, 1998, VISX, Incorporated of Santa Clara, California was notified that their photo-refractive PRK PMA P930016, Supplement S-5, for PRK for high myopia with and without astigmatism was approved by the Food and Drug Administration. This action expands their prior approved indications for low to moderate myopia with and without astigmatism to include PRK treatments for the elimination or reduction of moderate to severe myopia from minus 6 to minus 12 diopters spherical myopia at the spectacle plane, and up to minus 4 diopters of astigmatism.

The workload for fiscal year 1997 was as follows. Ninety-eight sponsors submitted documents on their IDE studies. That was 481 IDE submissions received or reviewed by this group of 7 individuals, plus a few others, in 1997.

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There were 45 original IDE studies submitted, 20 from manufacturers and 25 from sponsor investigators of manufacturers' lasers.

Seven PMAs and PMA supplements currently are under review.

Sponsor investigator IDEs from legally manufactured lasers--there are a number of sponsor investigator IDEs that were approved at the proposed clinical trials with a reasonable rationale and study design, provided adequate risk-benefit analyses and did not duplicate other trials for the same laser.

We emphasized that all applicants must follow the same regulatory rules.

A brief word about gray box lasers. Gray box lasers are lasers that were manufactured by VISX or Summit prior to PMA approval, distributed in foreign countries and then imported by users or their agents into the United States. They do not have the same software, hardware and the indications locked out as required by the PMA. They have been used on patients without an FDA-approved IDE or PMA.

On October 10, 1997, FDA gave owners of gray box lasers until January 15, 1997 the opportunity either to certify to FDA that the lasers are identical in all relevant respects to PMA-approved lasers, to disable them, or to

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submit IDEs for them. Subsequently, we determined there was no legal basis for certification. Most owners of these lasers have agreed in principle to dispose of these lasers; however, final disposition of them remains to be documented by FDA.

Black box lasers. Black box lasers are those lasers being used by individual practitioners to treat patients without an approved IDE or PMA. Often, the manufacturer was not identified. On October 10, 1997, FDA gave owners of black box lasers for refractive surgery until January 15, 1997 the opportunity to submit IDE applications to FDA, to conduct clinical trials to obtain clinical data on the safety and effectiveness of their lasers, or to stop using them and dispose of them or risk compliance action by the agency.

We were aware of several black box lasers at that time, of which a few had already submitted IDEs to FDA. Since January 15, 1997, we have approved 11 IDEs for black box lasers; we have documentation that some have been subsequently destroyed, and others have terminated their IDEs and are not enrolling additional subjects in their studies.

Black box lasers not under an FDA-approved IDE have been seized by FDA, have been destroyed by their

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owners, or have been disabled by their owners, awaiting final disposition. We are aware of a few black box lasers which are not under regulatory control, and the agency will continue to pursue compliance actions to ensure the law is obeyed.

Those owners who have chosen to have IDEs with FDA must follow the same regulatory rules and guidance for all IDE applicants. Owners of two of these lasers have submitted PMAs. The clinical data for one of these PMAs is being presented to the Panel today. FDA seeks your expert advice about the clinical data submitted to demonstrate a reasonable assurance of the safety and effectiveness of this device.

DR. McCULLEY: Thank you.

Are there any questions for Dr. Waxler?

Dr. Sugar?

DR. SUGAR: We reviewed guidelines at our last meeting, and I wonder what the status is of those revised guidelines.

DR. WAXLER: There has been no change, unfortunately; we have been busy, and we have not had--and I say "unfortunately," because I think it is very important to update these guidelines. We have a great deal of input from the Panel and other individuals, and we await the report

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from the two subgroups of the Panel that were to report. Hopefully, at the next Panel meeting, we can complete those issues and put out a draft for comment by the public. It has been just a bit too busy to finish it off. But thanks for asking.

DR. McCULLEY: No other questions?

[No response.]

DR. McCULLEY: If not, I would like to turn to Dr. Waxler to introduce the PMA.

DR. WAXLER: My comments are on PMA P970005.

The Panel's recommendation about the approvability of this PMA and FDA's decision will have no effect on the manufacturer of the Kremer Laser. This PMA is for a single unit. Neither LaserSight, which has announced a financial interest in this laser, nor the Kremer Laser Eye Center will be able to manufacture copies of this laser without additional data, engineering and manufacturing information. Also, approval of this PMA will have no effect on the status of LaserSight's scanning lasers or on off-label LASIK with other FDA-approved lasers.

Since this is a marketing application for laser-assisted in situ keratomileusis, LASIK, the PMA is for a system that includes two components--the laser and a microkeratome. The microkeratome component of the PMA is

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described in terms of its engineering and operational characteristics and not identified by trade name.

FDA monitors IDE and PMA applications for data integrity. There are no known data integrity problems with this PMA at this time.

The genesis of this laser is not germane to the Panel's deliberations today. FDA continues to review engineering and manufacturing information in this PMA. The agency brings this PMA before the Panel to seek your expert advice about the clinical data submitted by the applicant. Do you or do you not conclude that the clinical data submitted in this PMA demonstrate a reasonable assurance of safety and effectiveness of this specific laser system?

You are charged with making one of three recommendations to the agency: "approval without conditions"; "approvable with conditions," with a list of specific conditions; "not approvable," with a list of specific deficiencies.

Among the conditions you may consider if you recommend "approval with conditions" are cautionary labeling and additional follow-up data on any group of subjects for which you have concern. And you may request that this data be provided to the PMA or after approval.

This application stands on its own. Please do not

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compare it to other lasers for refractive surgery, either those that have received PMA approval or are under review. I urge each Panel member to use your own clinical knowledge and experience to arrive at your own recommendation as to whether there is a reasonable assurance of safety and effectiveness of this device.

In areas such as astigmatism, where there is no FDA guidance, you are urged to discuss fully the practical implications of any analyses, such as vector analyses, that have been conducted or that you may recommend be conducted--what are the implications for the patient? Can potential problems be addressed by cautionary labeling, or should the applicant modify the device to prevent such problems from occurring?

Ms. Jan Callaway is the Team Leader for P970005. She will give a brief introduction to this PMA.

Jan?

MS. CALLAWAY: Good morning. I'm Jan Callaway, the Team Leader for the PMA for the Kremer Excimer Laser Model KEA 940202. Photomed, Inc. of King of Prussia, Pennsylvania submitted this application, which was filed on January 31, 1997.

The sponsor is requesting approval for LASIK for primary myopia between minus 1 and minus 15 diopters, with

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and without astigmatism corrections ranging from zero to 5 diopters.

The Kremer Excimer Laser System is an argon fluoride excimer which produces pulses of 193 nanometer wavelength, with a fluence per pulse of 135 millijewels per centimeter squared, and an ablation depth per pulse of approximately .2 to .25 microns.

The primary Panel reviewers for this application are Dr. Marian Macsai and Dr. Joel Sugar. Panel input is required in this area because clinical judgment is required to evaluate the data. Your comments from the discussion today will help us in evaluating the safety and efficacy of the device for this indication for use.

The FDA team evaluating this PMA included the following reviewers. For engineer, Mr. Dennis McCarthy and Dr. Bruce Drum; for patient information labeling, Ms. Carol Clayton; software evaluations were done by Mr. Joseph Jorgens; bioresearch monitoring was supervised by Ms. Jean Toth-Allen; statistical reviews were done by Mr. Mel Seidman; and clinical reviews were done by Dr. Anthony Greer and Dr. A. Ralph Rosenthal.

I would like to thank these team members for the outstanding job they have done in their review of this document.

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The sponsor will make their presentation of the PMA at this time, followed by Dr. Rosenthal's discussion of his review.

At this time, I would like to introduce Mr. Michael Dayton, President of MEDTek Consultants.

DR. McCULLEY: Sponsor is aware that you have one hour for your presentation.

MR. DAYTON: Good morning. As Jan introduced me, my name is Michael Dayton, and I am a consultant with MEDTek Consulting, and I am the team leader for the presentation of the premarket approval of P970005 for the Kremer Excimer Laser Model KEA 940202.

First of all, we wish to thank the FDA and the Panel for inviting us here today to present these data in this Premarket Approval Application for their review and consideration.

Secondly, we'd like to apologize for our tardiness this morning, and we expect that we will take that off our presentation time so that we don't go over the one hour.

Another announcement--we have brought a copy of all of our slides here; it does not present new information that has not been seen or formulated in the PMA previously, so it is not new information. In addition, we have a couple of updated tables. There were several errors on some

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stratifications of the shift in cylinder for the lower stratifications, and we have that information. We could pass that out to you now, or if you'd like, we can wait until after the presentation. We brought the slides in case you wanted to write notes on specific slides to come back to you; so we can either hand that out to you now or after the presentation.

DR. McCULLEY: We'd like it now.

MR. DAYTON: Thank you.

[Documents handed to Panel members.]

MR. DAYTON: Before we begin, I'd like to introduce the individuals who will present to the Panel this morning.

[Slide.]

Ms. Maureen Lyden is President of Biostat International, a consultancy specializing in biostatistics and clinical trials research.

Dr. Frederic B. Kremer is a clinical ophthalmologist and principal investigator for the studies which support this Premarket Approval Application. Dr. Kremer is in private practice at the Kremer Laser Eye Center in King of Prussia, Pennsylvania.

And Mr. Michael Blair is an information management consultant for the Kremer Laser Eye Center, and Mr. Blair

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will manage the slide presentation for us today.

[Slide.]

Just as an overview of our presentation this morning, we'll go through the historical perspective as to why and how this laser has come to you today and how it evolved to become single-site laser for use at Kremer Laser Eye Center.

We will also talk about the device description, and we'll focus primarily on the laser system and patient management systems. As Dr. Waxler pointed out, the keratome, although used prior to the LASIK procedure, is not part of our labeling in that it is generic to perform an anterior lamellar section prior to the procedure, which is a well-known procedure and has been around for many years. And Dr. Kremer does go into some specifics about the generic mechanics of the keratome that he uses.

Next, we'll talk about the study protocol under which these data were collected, and after that, Dr. Kremer will summarize his clinical results for his clinical center and for himself and the second surgeon, whereafter he will summarize that information, where possible comparing endpoints to previously stated guideposts that the Panel has determined were appropriate for low myopic spherical correction without astigmatism.

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And then we'll draw conclusions from those data and subsequently, before we turn it over to the Panel for questions and answers, we'd like to briefly discuss proposed labeling.

Next slide, please.

[Slide.]

The Kremer Laser Eye Center is the sponsor for Premarket Approval Application 970005 for a single-site laser for use at the Kremer Laser Eye Center. As an explanation as to why a single-site approval is being sought, a bit of background history is in order.

Next slide, please.

[Slide.]

Before becoming an ophthalmologist, Dr. Kremer was trained as an engineer, receiving his master's degree in electrical engineering from Drexel University in 1972. He completed his medical degree at Thomas Jefferson University in 1976, and in 1980, he began performing corneal refractive surgery.

By 1982, Dr. Kremer began performing keratomileusis, and by the late 1980's, he had started work on developing an excimer laser for use in conjunction with corneal refractive surgery.

Next slide, please.

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[Slide.]

The reasons for developing a refractive laser--through his experience in refractive surgery and in an effort to provide the best possible care for his patients, Dr. Kremer came to believe that there was a need for certain design criteria relative to refractive laser surgery, one of which he felt there was a need for larger ablation zones than 4.5 millimeters in diameter, and also that ablation under the corneal surface as an alternative to surface ablation may be appropriate.

These circumstances led to his development of the Model KEA 940202 Excimer Laser and the subsequent submission of this Premarket Approval Application.

Next slide, please.

[Slide.]

The device itself is described, as I mentioned earlier, as two components. One is the laser head itself. It is a broad beam Excimer argon freon gas laser, operating at 193 nanometer wavelength. The laser repetition rate is 10 Hz, and the fluence at the corneal plan is 134 millijewels per square centimeter. The ablation zone used to treat myopic and myopic astigmatism is 6 millimeters in diameter, and the beam on modulation is accomplished through an expanding iris diaphragm with a rotating expanding slit.

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[Slide.]

The next portion of the device is a patient management system. In this case, there is an operating table with an adjustable, v-shaped headrest to stabilize the patient's head. The surgeon views the operative field and operative eye under an operating microscope, and the operative field is illuminated by a fiber optic light.

The patient fixates on a fixation light and focuses during the procedure. Two converging helium neon aiming beams intersect the center line of the microscope viewing axis, and this centerline viewing axis is also the centerline of the laser beam.

The microscope viewing area and the helium neon rangefinder aiming beams are the primary indicators for corneal alignment. More recently, a centration technique has been refined to also rely on geographic markers.

Next slide, please.

[Slide.]

The indications for us for use for the device, as you can see, is LASIK treatment of myopia ranging from minus 1.0 diopters through minus 15 diopters, with and without astigmatism, ranging from 0 to 5 diopters.

In addition, there needs to be evidence of a stable refraction as demonstrated by a less than one diopter

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shift over the one year prior to surgery.

And the patients need to be 18 years of age or order.

Next slide, please.

[Slide.]

The study design utilized to collect patient data for these studies was prospective, nonrandomized, unmasked, single-center, with two surgeons. We'll talk later on about comparisons between two surgeons regarding key safety and efficacy endpoints during the question-and-answer session, but because that would be new information, we would like to query the Panel on whether they would be interested in seeing those broken out that way at that time.

Pre- and post-operative measures performed by the co-managing doctor other than the surgeon--and that is one of the unique things about this trial that makes these data very real-world is that the co-managing doctors were trained to perform their responsibilities in this protocol and carry that out independently from the surgeons and those collecting and analyzing the data.

The co-managing doctors in this study are required by Kremer Laser Eye Center to execute a formal written agreement with Kremer Laser Eye, and as part of that agreement, they have to submit to Kremer Laser Eye the

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standardized pre- and post-operative case report forms for all patient visits--emphasis on "all"--and they must provide a CV and proof of licensure, and where possible and desirable, attend a course on LASER-K LASIK procedure.

[Slide.]

Further in the study protocol, there were two cohorts of patient eyes enrolled into this study. The first group of eyes were enrolled under a protocol approved by an institutional review board and were entered into the study from May 1, 1993 through June 30, 1996. The second group of eyes were enrolled under essentially the same protocol as the first group, but the protocol was approved by both the IRB and the FDA, resulting in IDE G9101. Eyes in the second group were enrolled from July 1, 1996 through November 20, 1997, at which time the database for both cohorts was frozen for data analysis. All subsequent analyses that have been done for the FDA and for our own purposes have been done on that frozen database.

There were minor changes to the protocol and the IDE, and those essentially were limited to--there were fewer intentional undercorrections performed under the IDE protocol. There was a total of 2,500 eyes enrolled into the two study groups.

At this time, I would like to turn the

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presentation over to Dr. Kremer to describe his LASER-K laser technique and summarize the clinical results.

Dr. Kremer?

DR. KREMER: Thanks, Mike.

Mr. Chairman, Panel and FDA members, ladies and gentlemen, thank you very much for giving us the opportunity to present our PMA application.

As Mr. Dayton noted, the driving force behind the derivation of this laser was to be able to treat patients in the best possible fashion. Based upon our experiences with other types of refractive surgery, particularly including keratomileusis with the cryolathe [ph], we felt that the LASER-K procedure--which is really just a name that we used to abbreviate "laser keratomileusis"--as you know, as time went on, the name that has really become associated with the procedure is the term "LASIK"--but we felt that such a procedure would have certain benefits for the patient, and over time, this has been shown to be the case.

[Slide.]

These benefits include that the procedure would preserve Bowman's membrane; it would be more comfortable for patients; they would have a more rapid visual recovery and more rapid refractive stability; it would avoid the need for extensive postoperative steroid drops; there would be a very

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low rate of infection and no observed late-onset corneal haze.

[Slide.]

The LASIK procedure, as you are already familiar, involves the creation of a corneal cap which is superficial. It is hinged to one side, and then the excimer laser beam is applied to the exposed stromal bed, and the hinged cap is then swung back into its original position.

Typically, the cap has a thickness of 160 microns, and it is created with a Ruiz microkeratome. The corneal bed is ablated to no closer than 200 microns from Descemet's membrane.

As was noted earlier, in the early part of the study, there was a higher use of intentional undercorrection.

[Slide.]

Preoperatively, patients had complete eye exams, including corneal topography; they had manifest refractions with fogging and visual acuity as part of those exams. The exam manifest refraction was tested and verified using a cycloplegic refraction.

Postoperatively, at each of the standard intervals--1, 3, 6, and 12 months--manifest refractions with fogging were performed, and there was an assessment made of

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the visual acuity and the safety level.

[Slide.]

Myopic enhancements were considered if the patient requested an additional procedure, if the setting was felt to be clinically appropriate, and if the myopia was greater than 1 diopter and/or the astigmatism greater than 1.5 diopter.

[Slide.]

We will now address the clinical results. First, we will look at the demographics, and then the accountability, effectiveness and safety.

[Slide.]

This slide summarizes the demographics, and you will note that in the IRB, or the first cohort, there were 1,140 eyes of 616 patients; in the second cohort, there were 1,360 eyes for a total of 2,500; and in the second cohort, that was of 714 patients. There were slightly more male patients than female. Age range was intended to be 18 as a minimum and up into the 70s as noted. There was one patient in the first cohort whose age was recorded just prior to her 18th birthday.

[Slide.]

This N-tree helps to assess the accountability at the 6-month postoperative interval. Of the 2,500 eyes that

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were treated on or before the freeze date of 11/20/97, there were 364 eyes who were not yet due for their 6-month interval; there were 10 eyes that were not eligible because they had hyperopic LASIK as an enhancement procedure; there were 5 eyes that were discontinued, typically because of having another procedure such as an astigmatic keratotomy.

I would like to note at this point that there should be one additional patient noted there as discontinued, who was a patient who, early in the study, had a large over correction and subsequent treatment with a keratophakia [ph], or corneal inlay enhancement procedure, who was actually included in the database but should be counted as discontinued.

So after subtracting those eyes, that leaves 2,121 eyes that are evaluable, and of those, there were 715 which missed the 6-month postoperative visit. There were also 4 eyes lost to follow-up. Our definition for this study of "lost to follow-up" is eyes that log more than 18 months from their last expected visit.

Now, we will see later that we have also studied the 715 eyes that missed the 6-month visit, and they fall into two groups--patients who were seen subsequent to the 6-month visit and patients who were not seen at the 6-month or later visit. But we have been able to study all of the

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eyes relative to the 6-month interval.

So in terms of accountability, we have the 1,402 eyes that we'll be able to review.

[Slide.]

This reviews the status of the 715 who missed their 6-month interval, and as we noted earlier, there were 10 not eligible, 9 from the IRB, one from the IDE; of the discontinueds, 4 in the IRB cohort, one in the IDE cohort, and so forth.

[Slide.]

This slide shows the last recorded best corrected visual acuity of the patients who are not eligible. The patient who is listed at 20/100 had a subsequent hyperopic LASIK enhancement and, following that procedure, has a 20/25 best corrected acuity, with a favorable refraction. The patient who was at 20/50 had a similar procedure, but continues to have a best spectacle corrected acuity that is at a level of 20/40; and the 20/40 patient had an enhancement procedure leading to a 20/25 result. So all of these patients ended up 20/40 or better.

[Slide.]

This shows the status of the discontinued patients, either 20/20 or 20/25 best corrected acuity.

[Slide.]

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Now, this leads to a 77 percent accountability at the 6-month visit, and if we look at the patients relative to 6 months or later visit, an 82 percent accountability.

We believe that the study is valid because 1) it has a very large sample size, and 2) there is no bias in those cases that were seen at the 6-month interval. And the reason we can conclude that is because we have studied all of the other eyes, 100 percent of the eyes, and although that comparison was not in the original submission to you, it is something that we can provide to you if we are given opportunity following the discussion.

I might add that there are several points in y talk where we have been able to look at the same data that you have but organize it somewhat differently, in a way that sheds more light on certain questions that have been raised relative to this application. So if I may, instead of saying that each time we come to a spot like that, I'll try to say the phrase, "If it's okay to present later in the discussion this morning."

[Slide.]

If we have opportunity to look at that information, you will see later that all of the cases are accounted for that were seen prior to 6 months and not seen in the 6-month interval and also those that were seen after

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the 6-month interval.

[Slide.]

In the IRB or first cohort, 16.8 percent of the eyes had enhancement procedures performed; 14 percent were myopic, 2.3 percent hyperopic. There was actually 0.4 percent that were myopic but had a larger than 6 millimeter ablation zone, and therefore are not part of this application.

In the IDE, there was a total of 4.9 percent enhancement rate, with 3.5 percent myopic and 1.3 percent hyperopic.

[Slide.]

Our application reads for the procedure to involve one or more LASIK procedures, and we want to note that there were three instances in the IRB or earlier cohort where the patient had two enhancements as opposed to one enhancement. And interestingly, all three of those were in a group that were also treated for astigmatism. And in the IDE, there were none that had a second enhancement procedure.

[Slide.]

We will now look at the efficacy endpoints. This slide addresses the stability of the manifest refraction. We used a definition of stability as recommended by the agency that the refraction not change by more than a diopter

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between the interval visits.

Using that definition, if we look at all eyes in the IDE cohort, 90.6 percent showed stability at the 1 to 3-month interval, 95 percent at 3 to 6, and 96.4 at 6 to 12. The earlier cohort did not show quite as high a level of stability.

We then stratified the stability based upon the preoperative refraction. So for patients who started with less than 7 diopters of myopia, we found a higher level of stability than for patients who started with greater than 7 diopters. However, the greater-than-7 diopters was still at the 91 percent level in the second cohort for the 3 to 6 months.

[Slide.]

We then addressed stability of cylindrical correction. We arbitrarily used the same definition, that is, that the astigmatism not change by more than a diopter in the two successive intervals.

In our initial analysis, we showed a high level of stability at the 3 to 6-month range, and we inadvertently showed less stability at the 6 to 12-month range.

We reanalyzed that and would, with your okay, like to present that later in the discussion this morning. That information will show that the stability is similar or

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actually higher when you go to the 6 to 12-month interval.

[Slide.]

In the information that has been in the submission, the stability for the second cohort, looking at astigmatism from the one to 3-month interval, was 96.4 percent and from the 3 to 6, also 96.4 percent.

[Slide.]

This slide addresses the level of uncorrected visual acuity being 20/40 or better postoperatively. If we first look at all eyes treated in the IDE or latter cohort, we see that this runs about 90 to 92 percent, depending on the postoperative interval--a little bit lower for the IRB cohort--and that is consistent with our original intention to undercorrect more frequently in the earlier cohort.

When we stratified by the 7-diopter preoperative refraction, we found that the patients who started out with less than 7 diopters had a 96.5 percent incidence of uncorrected vision of 20/40 or better at the 6-month postoperative interval in the second cohort. When we addressed greater than 7 diopters preoperatively, it was 73.3 percent at the 6-month postoperative interval.

Now, you will see that many of these slides will have a footnote noting that the outcomes that we observed met the previously-stated FDA guidelines for patients

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starting with myopia, that is, spherical myopia, with less than 7 diopters. I will avoid repeating that each time we go through these slides and simply note it when we go through our summary slides at the end of the talk.

[Slide.]

We assess predictability by looking at the difference between achieved correction in terms of manifest refraction, versus the intended correction. This was stratified by preoperative refractive error, and we found in the second cohort that 78.4 percent of the eyes ended up within plus or minus half a diopter of intended, 93.5 percent within plus or minus one, and 99.6 percent within plus or minus 2--somewhat less in the first cohort but very similar.

For those above 7 diopters, we found about 52 percent plus or minus a half, postoperatively, and 73.4 percent plus or minus one, and then 93 percent within plus or minus a 2 diopter range.

[Slide.]

We looked at the residual astigmatism for eyes that were treated for astigmatism. In our study, the astigmatism was treated if the preoperative magnitude was .75 diopters or greater; if it was less, the patient simply received a spherical-type correction.

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We found in the more recent cohort that there were 42.8 percent of the eyes with a residual cylinder of less than one-half diopter and another 26 percent that were between a half and one diopter; and additionally, 26 percent more between 1 and 2 diopters residual cylinder. And there were only in the second cohort 4.3 percent that were greater than 2 diopters residual astigmatism.

[Slide.]

We'll now look at the safety endpoints, first addressing the level of best spectacle corrected visual acuity.

Looking across the groups both at the 6-month and 12-month intervals for both the earlier IRB cohort and the later IDE cohort, there was no change in about 64 to maybe 67 percent, and then there were an additional maybe 7 to 10 percent where there was a gain in best corrected acuity of half a line or more.

We also observed a loss of half a line or more in between about 11 and 17 percent of cases, depending upon at what point in time we address it. There was a 2-line decrease in the most recent cohort, the IDE study, of 0.6 percent at the 6-month postoperative interval and zero at the 12-month postoperative interval. There was more than a 2-line loss of 0.6 percent at the 6-month interval and 0.7

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percent at the 12-month interval.

When stratified based upon the preoperative refraction, we see that patients who started with less than 7 diopters of myopia in the IRB study, there were no patients who had a best corrected spectacle acuity of worse than 20/40 at the 6-month interval, and in the IDE study, there were 0.2 percent.

When we look at patients who started out above 7 diopters, there were 4 percent in the IRB and 2 percent in the IDE. If we look at those patients more closely later, we find that in some cases, these acuities improved further when they got to the 12-month interval, and in some cases, they were decreased for reasons other than reasons related to the procedures.

[Slide.]

Grade 1 haze was noted in 3 eyes of the IRB study and one eye in the IDE cohort. There was not late-onset haze.

[Slide.]

We looked at induced astigmatism in eyes that were treated for spherical myopia. In the IRB cohort, we found 2.2 percent which had 1.5 diopter or greater induced cylinder, and in the IDE cohort, we found 6.3 percent, which was somewhat higher. In both cases, the incidence of

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induced cylinder over 2 diopters was quite low and well within the guideline. This prompted us to look more closely at the IDE cohort. We suspected that, based upon improvements that we had made in centration techniques when performing the procedures, this may have decreased, and we found that in fact it had decreased substantially, and if we have the opportunity, we would like to show that later in the discussion this morning.

[Slide.]

The occurrence of a flapless hinge--that is, a cap that has no hinge, or a free cap--occurred in 1.8 percent of the IRB cohort and 0.7 percent of the IDE cohort. Although listed as a complication, that was not associated with any impact on visual sequelae.

There were also 0.1 percent aborted procedures in the IRB cohort and 0.3 percent in the IDE cohort. We believe this was higher in the later cohort because of a slowly failing microkeratome.

Once again, these cases were subsequently operated on, and there was no visual sequelae from the pause in time interval. There was corneal edema noted at the one-week to one-month period in 5.3 percent of the IRB and 3.1 percent of the IDE cohort. There was no persistent corneal edema.

[Slide.]

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We looked for central epithelial defects.

Centrally, there was 0.3 percent in the IRB cohort, none in the IDE, and there was a peripheral epithelial defect in 0.2 percent of the IDE study.

We have also observed epithelium in the interface. If epithelium occurs centrally,, that generally does impact vision and needs to be removed, and we did so in .1 percent of the IRB and .1 percent of the IDE, keeping in mind that this report is for patients treated for primary myopia with and without astigmatism.

We also observed epithelium peripherally, which typically was isolated in nature, nonprogressive, and did not impact visual acuity, and therefore did not need to be removed, in 1.9 percent of the IRB cohort and 1.2 percent of the IDE cohort.

We also saw a low incidence of cap striae.

[Slide.]

We assessed patient symptoms following these procedures, and we have listed here the incidence of settings in which the patients felt that they had these symptoms to a bothersome degree. That would include bothersome glare, bothersome halos, difficulty with night driving, ghosts or double images, foreign body sensation, anxiety, and pain.

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We stratified these symptoms based upon their postoperative refraction and, as you might expect, they tended to be more prevalent in patients who had a larger residual refraction.

There was no attempt made in this study to assess the symptoms in the presence of spectacle correction for those residual refractions.

In the IRB cohort, the most prominent ones were bothersome glare at night, which was in 5.5 percent of the patients who had residual refraction of greater than half a diopter, and in 2.2 percent of those who had less than or equal to half a diopter of residual refraction.

We also saw difficulty with night driving in a similar incidence.

In the more recent cohort, the incidence of both the glare and the difficulty with night driving was lower. In this cohort, we saw ghosts or double images at 2.6 percent of patients who had residual refraction of greater than half a diopter.

In the IRB cohort, there was one patient who had an anxiety reaction that I will loosely define as someone who becomes concerned that they have had surgery, in some way gets fixated on that and has difficulty as a result. There was also one patient in the IDE cohort who was not

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seen at 6-month interval, but I think we should also note had a similar-type reaction.

[Slide.]

This slide reviewed the adverse events for the 6-month postoperative interval patients. It is important to cover adverse events at all ranges, so it is labeled, and I will make comments relative to other time periods.

There was one case in the IRB cohort where there was a corneal infiltrate noted. This was not of infectious origin and is believed to be cellular reaction around an interface foreign body.

There were no cases of corneal edema at the 6-month interval. However, at the one-month interval, as noted previously, there were two in the IDE cohort and 14 in the IRB.

There was one misaligned cap which was in the IDE cohort. This occurred one day postoperatively. It was repositioned and without visual sequelae. There were no lost or misplaced caps. There were no melted caps, nor any late onset of haze. There was one retinal detachment in each cohort--however, one occurred at the 11-month postoperative interval and the other at 12 months postoperatively, suggesting that these were not related to the surgical procedures.

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There were no retinal vascular accidents and no corneal infections.

[Slide.]

We have had an opportunity to compare the key safety and efficacy parameters for two different surgeons, and we hope to have opportunity to share that in the discussion later this morning.

At this point, I would like to summarize the key safety and efficacy parameters that we have already reviewed in the talk and in some instances reference them to the FDA Guideline.

We have addressed the patients having a level of 20/40 or better uncorrected visual acuity postoperatively. When we looked at that for all eyes in the IDE study, we saw 92 percent, and this slide shows the 95 percent confidence interval of 88 to 95 percent. When stratifying for the less-than-7 diopter cases, we see 96 percent having 20/40 or better without correction, well exceeding the FDA Guideline of 85 percent.

Manifest refraction postoperatively within plus or minus a half-diopter, in the IDE, looking at all eyes, is 72 percent. And it is interesting, for most of these if not all of them, even for all eyes, it meets the guidance for less than 7 diopters.

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For plus or minus a half, 72 percent for all eyes, and for less than 7, 79 percent, exceeding the 50 percent guideline level.

Working down, plus or minus one, we have 94 percent for those starting with less than 7 diopters; manifest refraction stability demonstrated at the 3 to 6-month interval were at 98 percent, exceeding the 95 percent guideline; best corrected acuity, loss of greater than 2 lines, there is some incidence, but well within the guideline.

This slide is for the spherical myopes, and you can appreciate there were none with less than 20/40 best corrected, no late-onset haze, and induced astigmatism above 2 diopters was very low.

[Slide.]

This is a similarly formatted slide for the patients who were treated for astigmatism, and if we go through each of the categories, first looking at those treated for less than 7 diopters, 97 percent uncorrected acuity, 20/40 or better; postoperative manifest refraction within plus or minus a half, 78 percent; manifest refraction within plus or minus one, 93 percent--all of these meeting the guidance, which is for less than 7 diopters. Stability of refraction, 96 percent; loss of greater than 2 lines,

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0.4; worse than 20/40, 0.4 percent; and no late-onset haze.

[Slide.]

This slide addresses the sub-cohorts of patients that had refraction greater than 7 diopters--that is, spherical equivalent refraction--preoperatively, again showing the 95 percent confidence level. And in this slide, we divided the groups between spherical myopes and those treated for astigmatism with or without myopic treatment, this being the first cohort, and this the second cohort.

The guidance that is listed here, of course, is for less than 7 because there hasn't been a guidance yet for greater than 7. And if we go down the list for the spherical myopes, 20/40 or better above 7 diopters preop, there were 77 percent; and for astigmatic, 70 percent.

Postoperative manifest refraction within plus or minus a half, 47 percent and 55 percent; within plus or minus one, 68 percent for the spherical myopes, 77 percent for the astigmats.

And stability for spherical, I think that's 88 percent, and for the astigmats, 93 percent.

Loss of greater than 2 lines, 3.8 percent and 2.7 percent; worse than 20/40, 1.3 percent and 1.8 percent. No late-onset haze. Induced astigmatism greater than 2 diopters, 2.6 percent.

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We feel that the patients who start out with greater than 7 diopters have a larger benefit when we assess the risk-to-benefit ratio prior to performing these procedures, and we feel that these are levels of safety and efficacy which are very consistent with a desirable risk-to-benefit ratio for the patients who are above 7 diopters.

[Slide.]

So in conclusion, we feel that our laser is safe and effective for treating myopia for minus-one to minus-15 diopters and for astigmatism up to 5 diopters.

[Slide.]

Our proposed labeling reflects those parameters that I just noted in terms of the degree of myopia and astigmatism. It should include that the patients had a stable refraction prior to surgery, as demonstrated by a less than one diopter shift during the one-year previous period, and who are 18 years of age or older.

[Slide.]

Contraindications include: active ocular/systemic infection; Fuchs' corneal dystrophy; keratoconus with thinning; central corneal scars affecting visual acuity; insufficient corneal thickness for desired power.

[Slide.]

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Warnings should include: ocular systemic infection--and the treatments may be considered after resolution of such infection; previous herpetic keratitis, in which case, the patients must understand the possibility of reactivation of the keratitis with resultant increased scarring and diminished vision; also, collagen vascular disorders. Patients would need to understand that sufficient data has not been generated to establish the safety in this area, and therefore, there is a higher risk level, and if consideration is given, that it should be considered on a monocular as opposed to bilateral basis.

[Slide.]

Precautions should include: severe dry eye syndrome; glaucoma; uveitis; blepharitis; psoriasis; immunosuppression; keratoconus without thinning; pregnancy, and systemic or topical use of steroids.

That will conclude this part, and I thank you very much for the opportunity to review these results.

DR. McCULLEY: Does that conclude your presentation?

DR. KREMER: Yes, sir.

DR. McCULLEY: Okay. Just so that we are clear, as I understand it, you are not allowed to present new data that has not been submitted to the FDA or distributed to the

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Panel. You alluded to several analyses, that it wasn't clear whether this was data that you had not presented or submitted to the FDA, or whether you were simply reworking submitted data. Reworking submitted data is admissible, and you still have 10 minutes in your presentation time; so if that's the case, then that is allowed.

DR. KREMER: Okay. It is strictly data that has already been submitted but has been formatted differently to look at in a different light.

DR. McCULLEY: That's perfectly acceptable.

DR. KREMER: We'll show that now, if that's okay. We will provide written copies of these as well and show them on the slides.

DR. McCULLEY: Dr. Waxler, would you like to comment--and I don't want to get out of order.

DR. WAXLER: No, you are not out of order.

DR. McCULLEY: So we're okay--and you're going to make sure that he doesn't get out of order, that this is all data that has been submitted.

DR. WAXLER: Yes.

DR. McCULLEY: All right.

DR. WAXLER: And I am sure Dr. Rosenthal will also be paying attention to what is going on, and he is well aware of the fact that this information is reworked data

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based on comments from the primary reviewers.

DR. ROSENTHAL: We were aware of this ahead of time, and we are happy for Dr. Kremer to present it. We would like him to present it during a time after my review so that he will have the opportunity to show what he presented to us and now what he is presenting to us. I've got that cleared with Dr. Alpert, and I think that that would be a better way to do it, and it would be more clear to the Panel on the issues on which he is making the new analysis.

DR. McCULLEY: As the FDA reviewer on this, we will follow your recommendation.

Okay. Now, the question is, Dr. Rosenthal, would you like us to take a break prior to your embarking on your review? This seems to be a reasonably auspicious time.

DR. ROSENTHAL: Yes, that's fine.

DR. McCULLEY: Please look at your watches, and let's take a 15-minute break, but an honest 15-minute break.

[Recess.]

DR. McCULLEY: If I could ask everyone to take their seats, our honest 15-minute break has become 20 minutes.

We are going to proceed with the FDA clinical review by Dr. Rosenthal.

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DR. ROSENTHAL: Mr. Chairman, ladies and gentlemen, first let me thank Dr. Kremer and Mr. Dayton for providing the data in a way which allowed me to analyze it easily and, I hope, intelligently and in a way in which I could raise the issues which I will raise during my presentation today.

I will not review the device or the data of safety and efficacy; that has all been presented to you, and it is all in the tables. What I would like to do is raise with you the issues that I think the submission raises, so that the Panel can see again those issues which I raised in my original review and which are still a part of FDA's concerns.

[Slide.]

The first issue has to do with accountability. These are the IDE protocol patients, all eyes treated, and as you can see in the lower right-hand corner, I have circled the number. The accountability, even if one looks at 6 months or later data, is only at 77.4 percent. Similarly, if one looks at the original group, the IRB group, even though that accountability is slightly higher, it is still at about 86.6 percent.

[Slide.]

So the question still stands, and it was the

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question which I asked originally--the accountability in this PMA is between--it should be 75 and 85 percent for both of the cohorts.

Previous Panel recommendations have required accountability to be around 90 percent. Does the Panel believe the large number of subjects reported in this PMA as well as the line item information concerning uncorrected visual acuity and best spectacle corrected visual acuity on the last reported visit of those who were not eligible or those who missed the visit which was presented in the addendum allows one to make a decision on safety and effectiveness at the reported level of accountability?

A comment about the line item information. It was summarized for the Panel and showed minimal problems with those individuals who either were not eligible or those who missed the last visit, the line item of the previous visit.

[Slide.]

One of the major issues in all refractive surgical procedures is the stability of the manifest refraction post-treatment. In the submission, the authors looked at all the patients who were seen at all the intervals, and in the IDE protocol, it came out to 139 patients; the stability was certainly above 90 percent, but on a small fraction of the total number of patients treated, around 1,300 in each

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group.

[Slide.]

And in the IRB protocol, the stability as defined by Dr. Kremer in his presentation was again at the 90 percent level, over the 90 percent level at between 6 and 12 months; but again, the number of patients who were analyzed was 304, which again was about one-quarter of all the patients treated.

[Slide.]

So those stability numbers, the denominator raised the issue that the stability results in this PMA were based on 139 patients in the IDE cohort with a capital "n" of 1,360 and 304 patients in the IRB cohort with a capital "n" of 1,140. These numbers are a small fraction of the total treated and represent only those subjects who were examined at all four postoperative visits. Is it reasonable to accept the stability percentages based on the numbers reported?

[Slide.]

The next issue has to deal with change in magnitude of refractive cylinder for eyes treated for spherical myopia. I have summarized it, my edition--at 12 months for the IDE patients, 6.8 percent have an increased cylinder of equal to or greater than 1.50, and at 12 months,

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45.8 percent have an increased cylinder of greater than or equal to .25 and less than 1.5. So that the total induced cylinder is over 50 percent.

[Slide.]

Similarly, in the IRB protocol, at 12 months, the induced cylinder of greater than or equal to 1.50 is 2.6 percent, and greater than or equal to .25 and less than 1.50 is 42.7 percent, giving a total of almost 45 or 46 percent. That to me raised the issue that the increase in cylinder which occur in eyes treated for spherical myopia ranges from approximately 50 percent to show an increase of greater than or equal to .25 diopter to between 2 and 7 percent, to show an increase of cylinder greater than or equal to 1.5 diopters--and is this of concern?

[Slide.]

Another issue raised by the submission related to the stability of the manifest refraction cylinder. In the IDE protocol, the change in cylinder magnitude between the various periods was calculated, and as you can see, the change of less than or equal to 1.00 diopters was 96 percent between one and 3 months, 96 percent between 3 and 6 months, but dropped significantly between 6 and 12 months to 74.2 percent. And a similar pattern was seen in the second group of patients, the IRB patients, in which this drop in

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stability between 6 and 12 months was even more significant. It dropped to 59.7 percent from a mid-90's level between one and 3 and 3 and 6 months.

So this drop in cylindrical stability between 6 and 12 months raised the question as follows. The data on stability of cylindrical correction based on manifest refraction in subjects treated for myopic astigmatism indicate a drop in the percent to change by less than or equal to 1.00 diopters between 6 and 12 months as compared to previous intervals. This was observed in both protocols. Does this indicate that the stability of the resultant cylindrical correction will continue to decline after 12 months, and if so, is further follow-up required either before or after PMA decision?

[Slide.]

The next issue that was raised in the submission had to do with residual cylindrical magnitude at 6 months post-treatment, and I'd like you to look mainly at the greater than 30 degrees. You can see that a large number of the residual astigmatic show an absolute shift in axis--33 percent between .5 and 1 diopter show a shift of greater than 30 degrees, 26 show a shift of greater than 30 degrees of those patients who had residual between 1 and 2 diopters, and 36 percent of those between 2 and 3 diopters show a

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shift of greater than 30 degrees. This is in the eyes treated for astigmatic myopia in the IDE protocol.

[Slide.]

The similar pattern is seen in the IRB protocol--again, please just look at the greater than 30 degree shift and note that again the numbers are quite high for greater than 30 degree shift in residual cylinder, .5 to 1.0, and high in all three categories greater than 1.0 and less than 2.0, and greater than 2.0 and less than 3.0, of between 40 and 50 percent.

[Slide.]

So that data raised the issue relating to shift in cylindrical axis. In the astigmatism myopes, approximately 50 percent in the IRB cohort and 33 percent in the IDE cohort demonstrate an absolute shift in axis of greater than 30 degrees at all residual cylindrical magnitudes. Is this of concern, and if so, how should this be addressed? Would any further studies be indicated?

[Slide.]

The next question that I raise, I won't show any data because it would be too complicated, because all the tables show data relating to retreatment. There were small numbers that had more than one retreatment, and the sponsor presents the data on retreatment as two or more LASIK

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treatments.

With regard to retreatment, should we ask the sponsor to present a breakout on subjects who have undergone higher numbers of retreatments?

[Slide.]

The next issue has to do with indications, and these are two complicated tables. They are the summary of safety and efficacy variables for the IDE protocol on all eyes, one or more LASIK treatments. But the issue is quite simple--that all the efficacy variables and all the safety variables--well, not all, but many of them--are much greater in the higher myopic range.

Just to give you an example, let's take 9.0 diopters, 9.0 to 9.99, and compare it to 2.0 to 2.99. The 20/20 or better in the 2.0 to 2.99 is 61 percent, and 20/20 or better in the 9.0 to 9.99 is zero percent. 20/40 or better is 98 percent in the 2.0 to 2.99, and 82 percent in the 9.0 to 9.99. The MRSEs are similarly not as good. The plus or minus 50 intended versus achieved is 68 percent in the 9.0 to 9.99 and 88 percent in the 2.0 to 2.99. And one can see this throughout the tables--if you go higher, the uncorrected visual acuity results are not as good, and the intended versus achieved are not as good.

The safety variables are small numbers. For

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example, here, you have 8 percent that have lost 2 or more lines of best corrected visual acuity in the larger group; here is one out of 15, whereas you see very few in the lower myopic range. And a similar case can be made in the IRB group of patients. Again, if we just do 2.99, here you have 53 percent 20/20 or better versus 15 percent in 9.0 to 9.99, and a similar pattern comes up, but the higher myopic range does not do as well, certainly in all the efficacy variables, and the safety issues are--there are potentially more safety problems, and in some of the safety variables, there are definite increases.

[Slide.]

So the sponsor requests treatment with the device in the range of minus 1.000 to minus 15.000 degrees of spherical myopia. Is this justified, and based on the data, should there be a different upper limit?

[Slide.]

The issue is also raised about the high myopes versus the low myopes. If one looks at the data stratified by dioptric group of less than 7 and greater than 7, Dr. Kremer alluded to that in his presentation--you might want to just see--I will show you the spherical myopes versus the astigmatic myopes in the IDE protocol. I am doing the IDE first each time. As you can see quite easily here, the

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spherical myopes have better results in less than 7 diopters than greater than 7, and the astigmatic myopes have greater results in the less than less than 7 than in the greater than 7 dioptic range.

[Slide.]

And if you look at the similar table for the safety and efficacy variables relating to the IRB protocol, you see a similar--the spherical myopes greater than 7 do not do as well in the efficacy variables as to the spherical myopes greater than 7, and the astigmatic myopes similar do not do as well as the astigmatic myopes, and the greater than 7 don't do as well as in the less than 7. And the safety variables, for example, here is 6.3 percent loss of 2 lines or more best corrected visual acuity in the astigmatic myopes and best spectacle corrected visual acuity of 5.8 percent in this group, versus minimal problems in the less than 7; but even in the spherical myopia, there is 3.2 percent loss of equal or greater than 2 lines.

[Slide.]

So it raises the question that if you feel that the results are acceptable and that approval is indicated for myopia greater or equal to minus 7, how should this labeling be approached, because I think it is very important that patients in the higher ranges be appropriately informed

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of the potential results.

[Slide.]

Finally, there was an addendum to the submission which the sponsors made in which they looked at a specific group of patients from the early treatment group, the IRB group. These patients were treated between, I think, May of 1993--I forget, but it was a consecutive period early on in the use of the laser, so it was 1993 and somewhere in 1996. This, they called the IRB Protocol Group 1, and in this group of patients, they actually have a rather good accountability at 6 months or later of 95.3 percent, and at 6 months of 90.5 percent. The "n" in this group is 483. So they have reasonable accountability in this group of patients which they call IRB Protocol Group 1--and remember, it was done early in the use of the laser, before the IDE was in operation, and it was part of the original IRB group.

[Slide.]

The key safety and effectiveness variables were also submitted to the agency, and you can see that the 6-month or later groups--I won't read them out, for brevity--but if you compare them with the total group or the IDE group that are reported, they are not as good, but remember, this was early in the course of the IRB protocol, and I think many undercorrections were being corrected, but

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I still think the numbers reach certainly a MRSE plus or minus .50 and 1.0 and 2.0 reach comparable guidelines of the agency, and certainly the safety variables are within the range of the agency.

So the question really is, with this group in which they have excellent accountability, can we use that data alone if the Panel does not feel that the accountability of the other data is not adequate, or can we use it as supporting evidence to bolster the accountability.

[Slide.]

So the final question is the big question: Based upon the clinical investigation, has this PMA provided reasonable assurance of safety and effectiveness of this single device for the correction of low to high myopia with and without astigmatism; and if not, does the Panel feel that a complete analysis of the IRB Group 1 eyes, in which they have quite good accountability of over 95 percent at 6 months and later, do they feel that the analysis by the FDA of this group would provide such assurance, since the only analysis we've got are the key safety and efficacy variables?

Thank you very much, Mr. Chairman.

DR. McCULLEY: Thank you.

Just so we know what's going to happen and in what

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order, we are going to have the two primary reviews next; then, we will invite the sponsor back to respond to questions that the panel will pose to you, and at that time, you will have the opportunity to provide clarifications and other analytical approaches that you have alluded to.

Dr. Macsai, are you first up?

DR. MACSAI: Yes.

DR. McCULLEY: Dr. Marian Macsai will present the first review.

DR. MACSAI: Mr. Chairman, Dr. Rosenthal, members of the FDA, members of the Panel, members of the audience, Dr. Kremer, thank you for giving me this opportunity to review PMA 970005, Photomed, Incorporated Kremer Excimer Laser Model KEA 940202.

This laser is proposed for the treatment of primary myopia with and without astigmatism, through one or more excimer laser in situ keratomileusis applications, which I will refer to as "LASIK."

To date, the laser has been used by Dr. Frederic Kremer and Dr. George Pronesti. The proposed indications are patients with myopia ranging between minus 1 and minus 15 diopters, with and without astigmatism, from 0 to 5 diopters.

The sponsors state the patients need to have a

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stable refraction over one year; however, in Volume 1, page 10, the inclusion/exclusion criteria are stated as "stable refraction defined as less than 0.5 diopter shift over the 30 days prior to surgery." The sponsor needs to clarify what they define as a stable refraction.

The contraindications to this procedure include active ocular systemic infection, Fuchs' corneal dystrophy, keratoconus with thinning, central corneal scars affecting visual acuity, and insufficient corneal thickness for desired power correction. In previous published study, exclusion criteria have included active ocular disease, keratoconus suspected by video keratography, connective tissue disorders, pregnancy, and previous refractive surgery. No publications have included any patients with keratoconus. Therefore, this contraindication requires some refinement.

The device is an argon fluoride excimer laser with a wavelength of 193 nanometers, pulse duration of 8 to 30 nanoseconds, and a rep rate in our handouts between 1 and 25 Hz with a fluence of 134 millijewels per centimeter squared and an optimal zone of 6 millimeters.

However, in Dr. Kremer's presentation, he states the rep rate is set at 10 Hz, and it is unclear to me what is the actual rep rate. One Hz is a bit slow, and one would

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imagine patients would have trouble maintaining fixation.

An excellent overview of the cohort has been given by Dr. Rosenthal in the Medical Officer's Report, so I will summarize only that which is pertinent.

There are some areas of the protocol which we are missing, such as the date at which enhancements were performed, details on patients who had prior corneal refractive surgery, and the criteria for enhancements, though the criteria for enhancements were presented to us this morning for the first time on Slide 16.

In addition, patients were evaluated at co-managing sites by qualified co-managing investigators. The sponsor needs to clarify whether or not these co-managers were working under standardized conditions and whether or not cycloplegic refractions were performed during the postoperative examinations. This is critical because cycloplegic refractions were performed preoperatively, though not stated on Slide 15, and if the sponsor is reporting attempted versus achieved correction or intended correction, these refractions must both be either manifest or cycloplegic. In addition, the report of a manifest refraction postoperatively is troublesome in young myopes with a high ability to accommodate. These patients may be overcorrected by one or more diopters yet have significant

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accommodation available to still achieve 20/20 uncorrected visual acuity while in their 20s and 30s. However, as these patients age, and their accommodative abilities decrease, they will have significant trouble with both near and distance vision if they have been overcorrected.

This is a critical point of standardization in this review, especially in light of the fact that in the patient accountability N-tree on page 14, in which 2,500 eyes were treated, 10 eyes were excluded initially due to hyperopic enhancement. I do not understand what hyperopic enhancement was performed and feel that patients who are treated for myopia and require a hyperopic enhancement should be considered treatment failures. This further raises my concern regarding the lack of postoperative cycloplegic refractions.

This also applies to the 5 eyes treated with astigmatic keratotomy that Dr. Kremer informed us about this morning and a patient treated with a corneal inlay.

There is some confusion in that in Slide 27, a total of 44 patients had hyperopic enhancements, and 7 had enhancement with a 6.5 millimeter ablation zone, though the laser is stated to have a 6 millimeter ablation zone.

[Slide.]

In previous reviews, a 90 percent accountability

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has been established as the standard according to the checklist of information submitted in an IDE application for refractive surgery lasers. In this IDE, the accountability does not exceed 88 percent at any time in the initial submission. And this is only if you accept missed appointments as part of the accountability. Missed appointments are defined as patients are only considered lost to follow-up by the sponsor if they have not been seen for 18 months since their last visit. This definition skews the accountability of this study.

A clear example of this is seen in Table 1, looking at uncorrected visual acuity greater than 20/40 at 6 months. IDE is Group 2, IRB is Group 1. I have separated the spherical myopes from the astigmatic myopes. The accountability in this chart appears to be quite good if you look at Columns 1 and 2 for patients less than 7 diopters and greater than 7 diopters. However, looking at the patients who were eligible for analysis and the actual patients who were examined at that time, the accountability appears to be quite low--somewhere between 41 and 62 percent.

As a result of this lack of accountability, it is extremely difficult to determine either the safety or efficacy of this device.

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Looking at the refractive parameters proposed by the sponsor, only 9 patients fall into the treatment group from minus 12 to minus 15 diopters of myopia. Also, preoperative cylinder was less than 3 diopters in 94 percent of eyes in the IDE and 96 percent of eyes in the IRB population. In light of this few number of eyes in these categories of myopia greater than 12 diopters and cylinder greater than 3, I am unable to determine the safety and efficacy of this device in those ranges.

An analysis of the best spectacle corrected visual acuity worse than 20/25, if 20/20 or better preoperatively, was 3.1 percent in the IDE group and 4 percent in the IRB group for spherical myopia with one LASIK treatment only. After two or more LASIK treatments, 5.6 and 5.3 percent of patients at 3 and 6 months, respectively, in the IDE protocol had a best spectacle corrected visual acuity worse than 20/25 if 20/20 or better preoperatively. In the IRB protocol, these numbers increase dramatically, to 13.5 percent at 3 months and 9.8 percent at 6 months, with 16.1 percent at 12 months.

Perhaps the sponsors could provide us with some important information on these patients, such as if this loss of vision was due to a regular astigmatism. This could be determine through a hard contact lens over-refraction.

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Centration may also play a role, and this information was not reported.

The guidance document states that less than 5 percent of subjects should lose more than two eyes of best spectacle corrected visual acuity.

[Slide.]

In Group 2, 11.1 percent of patients lost 2 or more lines of best spectacle corrected visual acuity at 3 months, and 10.5 percent at 6 months. The numbers reported as small, so it is difficult to know if these really are true percentages. If you look at the "n" here, we are talking about 41 patients in the IRB spherical myopes with two or more LASIK procedures.

Less than one percent of patients should have a best spectacle corrected visual acuity worse than 20/40, according to the guidance document.

[Slide.]

In Table 3, I have looked at best spectacle corrected visual acuity less than 20/40 at 6 months. Clearly, astigmatism and two or more LASIK are associated with worse results.

[Slide.]

If you look at best spectacle corrected visual acuity less than 20/25 at 6 months, as seen in Table 4, two

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or more LASIK are again associated with worse outcomes. In Cohort 2, where there were no intentional under-corrections, 5 percent of patients were reported as having two or more LASIK treatments. This number of patients requiring two more LASIK treatments appears to be higher than in previously published reports.

Another safety issue in this PMA as touched upon by Dr. Rosenthal is that 6.3 percent of the spherical myopes treated under the IDE cohort have an increase in cylinder of greater or equal to 1.5 diopters at the 6-month visit. I wonder, does this include the 5 patients originally excluded because they had astigmatic keratotomy. So is this really 6.3 percent, or could it indeed be higher?

This number increased to 6.8 percent at the 12-month visit, and the same pattern of increasing percentages of astigmatism in the spherical myopes was seen in the IRB cohort and raises the question of whether there is some continuous drift or trend toward increasing cylinder in patients who are treated for spherical myopia.

In Table 6.26.1(a), the revised copy provided today by the sponsors, 22.5 percent of patients treated for astigmatism less than one diopter ended up with more than one diopter of astigmatism.

[Slide.]

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As far as efficacy variables, the proportion of eyes that achieved uncorrected visual acuity of 20/40 or better at 6 months are summarized in this table. They do demonstrate that better than 95 percent of the uncorrected vision greater than 20/40 at 6 months--it is 95 percent for the spherical myopes less than 7 diopters in the IDE protocol and 77 percent for the spherical myopes greater than 7 diopters. However, the number of patients actually examined appears to be low.

The accuracy of correction appears to be greater in eyes with preoperative spherical equivalence of less than 7 diopters.

[Slide.]

In Table 5, the manifest refraction spherical equivalence at 6 months are summarized. In the IDE group, two or more LASIK are associated with worse outcomes.

Stability of manifest refraction demonstrates the eyes with preoperative spherical equivalence of less than minus 7 diopters are more likely to achieve and maintain stable spherical equivalent than eyes with preoperative spherical equivalence greater than 7 diopters.

Regarding adverse events, the adverse events reported are low for both the IRB and IDE groups and appear to be lower than those reported in previously published

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studies.

Retreatments--this section of the PMA remains unclear. Ten patients were originally excluded due to hyperopic retreatments, presumably for overcorrection. In addition, under the IDE protocol, 19 eyes were treated for overcorrection, and 48 eyes were retreated for undercorrection. Therefore, the overall enhancement rate in the IDE protocol was 49 percent--67 out of 130.

Yet it was reported by the sponsor that only 67 out of 1,360 (5 percent of patients) required two or more LASIK treatments.

Under the IRB protocol, 5 eyes were retreated for overcorrection, and 158 were retreated for undercorrection, for an overall enhancement rate of 16.1 percent. After retreatment in the IDE group, 69 percent of patients were less than 7 diopters and plus or minus 1 diopter, and 27 percent of those greater than 7 diopters were plus or minus 1 diopter. However, 20 percent of those greater than minus 7 diopters in the IDE group lost 2 or more lines of spectacle corrected visual acuity. Thirteen percent had best spectacle corrected visual acuity less than 20/40, and 22 percent had an increase of greater than 2 diopters of cylinder, as seen in Table 6.6.1(c). In the IRB group, 85 percent of those less than 7 diopters were plus or minus 1

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diopter, and 73 percent of those greater than 7 diopters were plus or minus 1 diopter, with only 5 percent losing 2 lines best spectacle corrected visual acuity.

As far as specific user training restrictions, over 90 percent of these procedures were performed by one surgeon; therefore, safety and efficacy of this PMA can only be judged on the basis of use of this device by the sponsor. I would not recommend use by other surgeons until significant data is presented demonstrating safety and effectiveness of this laser in other users' hands. The data from the second surgeon was not separated out from the first, making this analysis impossible.

In summary, the data presented represents results on a limited number of patients due to lack of follow-up. The high number of retreatments, some of which are hyperopic, are worrisome. The necessity of retreatment should be very low in the IDE protocol due to no intentional undercorrections, yet there were high, and it appears that two or more LASIK are associated with worse results.

The problem is it is very difficult to analyze this study as there are very few in the literature to compare it to.

Subsequent to my review, I received more data from the sponsor on patients in Group 1 from the IRB protocol. As

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discussed by Dr. Rosenthal, these are patients treated between May 1, 1993 and June 30, 1995. They have included all eyes examined at 6 months or later in this group, and the sponsor reports on 92 percent of patients. Again, 10 eyes are not eligible for analysis because they received hyperopic enhancements. I still consider these patients to be important in the analysis because a hyperopic enhancement is done for an overcorrection.

The number of eyes with best spectacle corrected visual acuity less than 20/25 who started out with 20/20 preoperatively is still very high in this Group 1. Looking at all eyes, it is 5.8 percent. And I'm not sure if this should include the 10 hyperopic overcorrections and the 5 patients who had AK, because I don't have data on these patients.

If you look at all patients with just one LASIK, only 4.7 percent had best spectacle corrected visual acuity of worse than 20/25 when they started out with 20/20, and 10 percent with two or more LASIKs.

Separating the spherical myopes and the astigmatics with two or more LASIKs, these percentages still remain high at 11.8 percent and 9.1 percent.

In summary, I have tried to fairly determine the safety and efficacy of this device; yet the data has changed

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so rapidly that this is extremely difficult. There are a number of areas of concern, and conflicting data appeared on slides this morning to that received prior to this meeting. Clearly, this limits my ability to review the PMA in detail, and I would urge the sponsors to organize the new information and forward it to the agency.

Thank you.

DR. McCULLEY: Thank you, Dr. Macsai.

Dr. Joel Sugar has the other primary review.

DR. SUGAR: Anything I say is going to be redundant, but I am going to do it anyway--but I'll try to do it briefly, and I'm going to skip some of the boilerplate.

The specifics of the study were not presented to me as a reviewer, and it is uncertain what the data sources were. As the sponsor stated, many of the patients came from other locations including other countries and were not followed by the principal investigator. Whether data acquisition was carried out in a standardized manner was not specified. The accountability is a concern, and we went through that.

Given the uncertainty of the data sources and the relatively low accountability, I am left with great concerns. The inclusion criteria are also an issue. While

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keratoconus with thinning was an exclusion, it is uncertain whether patients were screened by video keratography for keratoconus--apparently, they were not--for keratoconus without obvious corneal thinning, and whether any such patients were included in the study. There is also no exclusion for prior corneal surgery, and it's uncertain whether patients were entered who had undergone previous radial keratotomy or PRK. In addition, no specifics are provided to the type of keratome used, the depth of the keratome cut, or the depth of ablation prior to a slide that was shown today, so they were asking for approval of a system and a device without even naming the specifics of the device.

The statement is made, however, that no ablation depths were closer to the endothelium than 200 microns. No data on cycloplegic refractive outcomes or acuities were provided.

Given these limitations, the safety was relatively good, except for the issue of induced astigmatism. Induced astigmatism of greater than 2 diopters occurred in only .6 percent of the IDE patients with spherical myopia at 6 months and .3 percent of the IRB patients in the same time frame. Of greater concern, however, 6.3 percent of the IDE patients and 2.2 percent of the IRB patients had increase in

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cylinder of greater than 1.5 diopters at 6 months.

In the IDE group, of those patients with less than or equal to one diopter of preoperative cylinder treated for astigmatic myopia, 23 percent have one diopter or more of astigmatism after treatment. Similarly, in the IRB protocol, 29.8 percent of the comparable group ended up with one diopter or more of post-treatment astigmatism.

This and other evidence of significant induced cylinder raise questions about centration. There are no data provided on centration, and it would be of interest to know if topographic analyses were done and whether these analyses provide information on the source of the induced cylinder.

Adverse events were low, and significant haze was minimal. Data in induced hyperopia is not specifically provided, and there is no data on cycloplegic refractions provided, and all refractive outcomes are reported in plus or minus form, without specifically listing hyperopia.

The enhancements have been discussed, but enhancements for other reasons such as epithelial ingrowth were not discussed, and we do not know the total number of patients who had additional operations after their first LASIK.

The frequency of patient symptoms including glare,

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halos, difficulty with night driving, double vision and ghosts were low in both cohorts, and while these are probably acceptable, the specific frequencies need to be mentioned in the patient and physician information booklets. Other complications, including hingeless or free flaps, were low.

Concerning efficacy, very few patients over 13 diopters were evaluated, and the outcomes in patients over minus 9.99 diopters were significantly worse, especially in the IDE protocol, than in patients with less myopia. Likewise, the numbers of patients with cylinders over 4 diopters were insufficient for analysis.

The labeling is insufficiently specific concerning exclusion criteria. In the absence of data to suggest otherwise, keratoconus patients should all be excluded. In the absence of data concerning patients who have undergone prior corneal surgery, these patients should be excluded. Specific data on overcorrection should be stated in the labeling for both physicians and patients. Epithelial ingrowth should be added as a possible cause for decreased vision.

There are some specific changes in the physician booklet on the size of the canula; in two different places, they talk about different sizes of canula used for drying

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the edges, and I don't need to go through that.

An interesting statement is made on page 453 that, quote, "Laser-K procedure can correct all degrees of nearsightedness and astigmatism. This is in the patient information booklet." Certainly, this statement should be eliminated, and a data-related specific statement should be made.

Nowhere in the physician and patient information booklet is there a discussion of specific risks related to unilateral versus bilateral surgery, but that, we have decided is a practice of medicine issue, and we don't need to discuss that further.

Given the insufficient information provided, and given the significant induced cylinder, I do not feel that this PMA warrants approval.

DR. McCULLEY: Okay. In the proceedings now, what we would like to do is invite the sponsor to return to the table and FDA to retire from the table. We will now have an opportunity for Panel members to ask questions of the sponsor, and I will start off with a question so that we keep the proceedings appropriate.

I have a question for Dr. Kremer. You mentioned data that you had reanalyzed, which was data that had been presented, not new data--and that's important, and I am

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going to count on the FDA to be certain that the data that is being presented is data that has been submitted and is being analyzed in a new format--and I'd like to ask you to present that data to us at that point.

DR. KREMER: Thank you. We'll just go through those in the order that we have them. We can provide these with paper copy for the Panel to follow along, if that's okay.

DR. McCULLEY: Yes, that would be helpful. Possibly, that can be handed out while you are speaking.

DR. KREMER: Okay. The first comment with regard to accountability. I mentioned earlier that although the accountability at the 6-month interval was at 77 percent and at 82 percent if we looked at patients who were seen at 6 months or later, we further studied the patients who were not seen at the 6-month or later interval, and if we can go to that slide, as you look at the handout, that's the one that you have first. We basically found that with one exception, there was no statistically significant difference among the three groups of patients, and this is when we examined the key safety and efficacy variables.

The patients who did not get seen at 6 months or later is one group, the patients seen at 6 months is a second group, and then, thirdly, the patients who missed 6

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but were seen subsequently. The Chi-square and p-values are noted on the right side of that chart--hopefully, we'll have it on the screen in a moment. The one area that did have statistical significance was the measure of the percentage of cases within plus or minus a half and plus or minus one diopter, compared to intended refraction. And in both of those cases, the other two groups actually showed better results, not worse.

Let me see if I can home in on this on the screen here. There are two low p-values here; they correspond to plus or minus a half and plus or minus one. And I think you can appreciate that with each of these safety and efficacy variables--that is, 20/20 or better without correction, 20/40 or better without correction, loss of greater than or equal to 2 lines best corrected, worse than 20/40 vision, and increase of greater than 2 diopters cylinder, end vision worse than 20/25--all three groups are statistically the same. We think that that demonstrates that there was no bias in looking at the patients studied at the 6-month interval.

DR. MACSAI: Can we ask questions?

DR. McCULLEY: Yes, you can ask questions.

DR. MACSAI: Dr. Kremer, I am a little confused.

What do you mean by "missing"?

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DR. KREMER: There is a window defined as the 6-month postoperative window. If a patient was not seen in that interval, then they are not counted as having had a 6-month visit, and they in turn make the accountability lower.

DR. MACSAI: So are these the lost to follow-ups?

DR. KREMER: No, they are not. I understand the confusion. The term "missing" here is not intended to mean a missing patient; it is intended to mean that they missed or did not come in for the 6-month postop visit.

DR. SUGAR: Can I ask another question?

DR. McCULLEY: Yes.

DR. SUGAR: Why are the n's different in the first 2 lines from the next line?

DR. McCULLEY: Dr. Kremer?

DR. MACSAI: Monovision.

DR. KREMER: Because the patients--thank you--there were certain patients who were excluded from the 20/20 and 20/40 analysis because they were planned as monovision or intentional undercorrection patients. So that decreases the "n" for them, but they are included in the other safety analyses.

DR. SUGAR: Thank you.

DR. MACSAI: So what--

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DR. McCULLEY: Please be recognized and state your name.

Dr. Macsai?

DR. MACSAI: So the question I have is pretty simple here: We are looking at how many total patients in this chart? It looks like about 960, 970.

DR. KREMER: Well, there are actually two corresponding charts. There is one for the IDE, and on the back of that page is the one for the IRB cohort. And--

DR. MACSAI: But I guess I have a simple question. Does this address the patients whom we don't know anything about? Yes? No?

MS. LYDEN: This is Maureen Lyden speaking. It addresses that patient that we don't know about at 6 months who have missed their 6-month visit. We do have visits for them prior to 6 months, and that's the column that you see on the left, that they have missed the 6 months but their last visit was before them, which means either a 1-month or a 3-month visit, and we've taken their last status and compared that to patients who did come in for 6 months. And the other group on the right are those patients who missed 6 months but came in subsequently.

DR. MACSAI: I understand that, but this is about 900-some patients--I'm not that good at the math--and there

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were about 1,300 patients in this group.

MS. LYDEN: But these are out of those that are just due for 6 months.

DR. KREMER: They have to be due for the 6-month interval.

DR. MACSAI: So there were 400-some who were not yet due.

DR. KREMER: Three hundred sixty-four. They were noted earlier in the talk.

DR. MACSAI: Okay.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I just want to make sure I got the columns right. So the 6-month column is the patients you've previously reported in the IDE--

DR. KREMER: Yes.

DR. BULLIMORE: --on the PMA.

DR. KREMER: That's correct.

DR. BULLIMORE: The third column is basically patients who missed their 6-month visit but have subsequently been examined?

DR. KREMER: Yes.

DR. BULLIMORE: Okay. Thank you.

DR. MACSAI: So it's new information?

DR. McCULLEY: Dr. Macsai--shape up.

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[Laughter.]

DR. McCULLEY: Now you may speak.

DR. MACSAI: So have you found these patients and reexamined them since you submitted this IDE--

DR. KREMER: No. All of this data is--

DR. MACSAI: --or where did they come from?

DR. KREMER: --all of this data is in your original submission, and it can be found--if you look through the tables, you'll note that in the submissions, the postoperative information is reported at periodic intervals--3 months, 6 months, 12 months and so forth.

DR. McCULLEY: Okay. Dr. Bullimore?

DR. BULLIMORE: I just have one other question. You're using the Chi-square statistic. I assume you are comparing the proportions in the three columns?

MS. LYDEN: Yes, that's correct.

DR. BULLIMORE: So if we look at the safety variables, for example, the second one, the best spectacle corrected visual acuity worse than 20/40, you have a p-value which is sort of approaching statistical significance, but it is unclear what's driving that p-value, whether it's because the third column, the 2 out of 85, is a higher percentage or whether the first column, the zero out of 228, is a lower percentage.

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MS. LYDEN: Individual pair-wise comparisons are not presented--

DR. McCULLEY: Please identify yourself.

MS. LYDEN: I'm sorry. Maureen Lyden. The individual pair-wise, comparing each column to the 6-month present column were not presented on this table.

DR. BULLIMORE: I am just trying to make sure that the numbers we are being presented with are--

MS. LYDEN: It's referring to a difference found among those three groups.

DR. BULLIMORE: Okay. Thank you.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: Dr. Kremer, what I would like to know is your study plan was to look at patients at one, 3, 6 months postoperatively and one year postoperatively; yet we see from the data that you had to add patients later on who didn't have the 6-month data and so on. Why wasn't your original protocol followed carefully?

DR. KREMER: The original protocol was followed. At the agency's recommendation, based upon the demonstrated stability, we did our analysis at the 6-month interval.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: Yet there was a significant number of patients who weren't there at the 6-month interval.

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DR. KREMER: Oh, yes. Our experience has been that patients who have refractive procedures tend to be young and mobile and not have other health problems, and it is quite difficult to get them to come in for follow-up visits. In the earlier part of our study, we did this extensively through the use of telephone calls and postcards and so forth, and we continued in this part of the study to also do that, but it is very difficult to get these people to continue to come in for all of these visits when they are happy with their results, they are mobile and perceive that they do not have a problem.

DR. McCULLEY: Is it fair to say, then, that you demonstrated your ability to have good accountability in your Group 1?

DR. KREMER: Yes.

DR. McCULLEY: But it was not carried forward and demonstrated in the IDE.

DR. KREMER: The accountability was not as high in the IDE cohort as in the first cohort.

DR. McCULLEY: Okay. Do you have more slides?

DR. KREMER: Yes. Let's go to the next one.

DR. McCULLEY: We don't have a specific time limit on this, but we do need to be aware of the time, so if you could move forward, please.

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DR. KREMER: Let's skip through these specific ones. I want to go further down. I want to go to the ones where the patients were present for cylindrical correction at 1, 3, 6 and 12 months--yes, there we go.

[Slide.]

Okay. With regard to the stability of cylindrical correction, we felt, too, that in the initial analysis, it appeared that there was a decrease in stability of the cylindrical corrections between 6 and 12 months. However, we realized that in the initial analysis, we had not isolated cases that were examined at each of the postop visits, and when we went back to do that--that is, requiring that the postop patients for whom we were assessing cylindrical stability were present for all of the 1, 3, 6, and 12-month visits--we found that the stability actually did increase between the 3 and 6 and 6 and 12-month intervals. So in actuality, the stability of the cylindrical corrections is quite stable.

DR. McCULLEY: Do the Panel have questions on this issue? Dr. Bullimore?

DR. BULLIMORE: Could you give us the original data table or slide number that this is meant to be compared to? I've got so many copies of this now, I'm getting lost.

DR. KREMER: Do we have that in the index?

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DR. BULLIMORE: Please move along if there are no further questions, but I would like to know that.

DR. McCULLEY: Dr. Macsai--someone was moving at that end of the table. It's dark--I can't see--no.

Dr. Pulido?

DR. PULIDO: Yes. Dr. Kremer, I'd just like to say that there were so many submissions with so many appendices, it was very, very difficult to follow all the data with so many different submissions that were made, and I think it really should have been done a little bit better.

DR. KREMER: Thank you.

DR. McCULLEY: Okay, point made. Do you have the data? I hate to let Dr. Rosenthal get close to that overhead. Would someone put Dr. Rosenthal's overhead up, please?

[Slide.]

DR. McCULLEY: Would you like to comment on it, Dr. Rosenthal?

DR. BULLIMORE: I think that'll do it.

DR. MACSAI: That's IDE; weren't you talking about IRB?

DR. BULLIMORE: No; I want the IDE.

DR. McCULLEY: Is this what you're looking for, Dr. Bullimore?

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DR. BULLIMORE: Yes, I think so. I'm just trying to make sure that the numbers are consistent, at least in my own mind. What we're looking at here is the IDE cohort, the eyes treated for astigmatic myopia, and I assume this is meant to be the equivalent table to Table 3.2(a) which has just been distributed to the panel.

The table that Dr. Rosenthal presented earlier has 69 out of 93, and the one that the sponsor has just presented to us has 90 out of 92, and I'd just like to know why the numerator and the denominator are both changed in opposite directions.

MS. LYDEN: What we did when we submitted it in the PMA was we required in this particular table that they only have 1, 3, and 6 for the first two columns to compare those. As you can see, there were fewer patients in the 6 to 12 interval there. If we looked at all 1, 3, 6, and 12, we lost quite a few trying to make an assessment of 1 to 3 and 3 to 6; so we kind of separated the analysis of 1 to 3, 3 to 6, and then 6 to 12 was somewhat different. And they are not necessarily the same people, so we agree that it was fairly confusing to try to follow it; that's why we just redid it now with 1, 3, 6 and 12 all being required, so we can make an assessment.

It's hard to make a jump from 3 to 6 and 6 to 12

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in this table, because they are not necessarily the same folks.

DR. McCULLEY: Dr. Macsai?

DR. MACSAI: So this analysis you are presenting is on the 72 patients who actually managed to be seen at 1, 3, 6, and 12; is that correct?

MS. LYDEN: Oh, he's in the new one. Yes, that is correct.

DR. MACSAI: So it's only 72 patients out of 1,000-some--72 eyes out of 1,000-some eyes.

MS. LYDEN: Well, it would be out of those who would be eligible to be in this analysis, which would be those who are due for a 12-month visit. You could never have a smaller population than that ever being in this type of analysis, because you need to have those that would be due for 12 months.

DR. MACSAI: How many were actually due for 12 months--72?

MS. LYDEN: No, no. It's probably on the order of--it's small--it's probably around 10 to 20 percent, I'm sure, patients available.

DR. MACSAI: So between 120 and 240? I'm confused.

DR. McCULLEY: Can we have the lights back on,

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please?

DR. MACSAI: It would be helpful to know what percentage of eyes were actually due for this 12-month visit, made it and are in this analysis. Does this represent 10 percent, 90 percent, or what? I'm not sure. I can't figure it out from the way the data was presented to me.

DR. McCULLEY: Was that data submitted originally?

MS. LYDEN: Yes. You'd find it in the accountability table as far as who would be available for 12 months in the astigmatic group in the IDE study.

DR. McCULLEY: And can you provide that?

MS. LYDEN: Yes. That's in Amendment 18, page 7. So just doing a quick calculation, it looks like 240 patients are eligible to be in that analysis, so it's--71 out of 243 is actually the accountability for that analysis, because 243 are the only ones that would be--

DR. MACSAI: So this is roughly 33 percent.

MS. LYDEN: Yes, that's correct.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I think Dr. Macsai has sort of zeroed in on the issue of accountability. I'm just trying to compare the table presented by Dr. Rosenthal and the one that is just being presented to us now, because according to

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Dr. Rosenthal, there are--I don't want to change media again--but can you give us the numbers, or can you give me the table so I can--I'm going to get a headache from the lights going up and down.

MS. LYDEN: This is page 258 in the PMA, Amendment 815.

DR. BULLIMORE: So the numbers I am trying to compare in Dr. Rosenthal's overhead, which is indeed page--no, that's a different one--this is just for the IDE subjects--according to Dr. Rosenthal's table, which presumably was taken from the original submission, you have 69 out of 93 subjects that change by a diopter or less. That means that 24 subjects changed by more than a diopter.

The table we have just been presented with here shows that in fact only 2 changed by more than a diopter. I just want to know what happened to those 22 subjects. Were they reanalyzed? Were they now excluded from this analysis?

MS. LYDEN: Yes. They were excluded from the second analysis because we required that they also have 1, 3, 6, and 12, and in the first table, they were only required to have a 6 and a 12 to be there. It was kind of comparing apples and oranges the first time around. So that's why we redid it.

MS. THORNTON: Yes, Dr. Rosenthal?

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DR. ROSENTHAL: In this new table, if they had to be seen at 1, 3, 6, and 12, why is the denominator not all 92?

DR. BULLIMORE: I'm sort of happy to move on.

DR. McCULLEY: Do you have any further slides or any other information that you alluded to before, relative to the issues you brought?

DR. KREMER: Yes. We want to look at the induced cylinder for patients treated for spherical myopia.

DR. McCULLEY: Excuse me. I had asked a question before that asked you to provide the data that you had alluded to.

DR. KREMER: Yes.

DR. McCULLEY: Is that what you are still doing--

DR. KREMER: Yes, sir.

DR. McCULLEY: --or are you going on to other issues that were brought up during the discussion and the reviews?

DR. KREMER: No. This is still what I alluded to in the earlier presentation.

DR. McCULLEY: Okay. Please proceed.

[Slide.]

DR. KREMER: From the clinical standpoint, we had found that we were able to improve our centration techniques

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when performing these procedures, and we went back and looked at cases in the more recent part of the IDE cohort, specifically, patients who were treated after 5-1-97, and we looked to see to what extent there was induced astigmatism in this group. It turned out that there was in fact less induced astigmatism with the improvement in centration with the surgical technique.

The sheet that you have shows the at the one-month postoperative interval, 3 months, and 6 months. And if we just look at the one-month postoperative interval, there is one case that has an increase of 2 diopters--

DR. MACSAI: Excuse me, Dr. Kremer.

DR. KREMER: Yes.

DR. McCULLEY: Dr. Macsai.

DR. MACSAI: I never received any separate data on patients treated after 5-1-97. Unless you could refer to where that was, I can't give this a fair analysis.

DR. KREMER: This is a subgroup--do you want to just go ahead?

MS. LYDEN: This is a new analysis--

DR. McCULLEY: Identify yourself. Did the FDA receive this data? Understand that we're trying to be fair, but we have rules under which we must work, and one of the rules is that you may not submit or present new data not

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previously submitted, and Dr. Macsai has raised the issue that she did not see that. Did the FDA receive this information?

MS. LYDEN: This particular slide--no.

DR. ROSENTHAL: No, it did not.

DR. McCULLEY: Then, that's not submissible, as I understand.

DR. ROSENTHAL: This is a subgroup of patients, and I don't think it's appropriate.

DR. McCULLEY: Then--I'm sorry--it's not submissible. So please take the slide off and turn the lights back up.

DR. KREMER: We'll move on to the next slide, which is the surgeon comparison.

[Slide.]

DR. MACSAI: Excuse me, Dr. Kremer. Again, I did not receive separate data on your and Dr. Pronesti's results prior to this review--unless you can tell me where it was; maybe I missed it.

DR. KREMER: We may have had somewhat of a misunderstanding in that in the previous slide as well as this slide, I suppose, the data that's in the slide is in the initial submission, but it's not broken out in the way that it's broken out in these two slides. It is a different

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format of data that has been provided but not provided in this format.

MR. DAYTON; Excuse me. During our presentation, we alluded to that we had taken data that was from the frozen database from which the PMA was analyzed and submitted to the agency and Panel. That is the same information from which these new tables are derived.

What we were alluding to in our presentation and not wanting to forego protocol was to not present that information without first receiving the Panel's permission. That's what we thought we had done just before presentation of this, and Dr. Rosenthal thought that it may be appropriate that we could do so, identifying this as new breakout.

If that was an incorrect understanding on our part, we--

DR. McCULLEY: I think I have stated clearly my understanding of the rule, and I guess what we need to do is possibly ask Dr. Waxler to return to the microphone and clarify whether this is data that had been previously submitted to the FDA and is therefore submissible here. If it has not been previously submitted, as I understand it, then we've got to stay with the rules, whether they are good for you or bad for you.

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If this had been submitted, it is allowable; if it has not been, it is not.

DR. WAXLER: A moment of consultation.

DR. McCULLEY: Okay.

[Dr. Waxler and Dr. Rosenthal conferring.]

DR. McCULLEY: Dr. Pulido, while the FDA is consulting.

DR. PULIDO: Just a point of clarification, too. Supposing that the previous slide was acceptable, had there been a change in protocol? You're telling me that there was a change in protocol; is that true?

DR. KREMER: No. It shows that the outcomes for the two different surgeons--

DR. McCULLEY: Wait. Point of order. We should not be discussing something that is not submissible.

DR. KREMER: Fine.

[Pause.]

DR. KREMER: The referees have huddled.

DR. WAXLER: The data was presented in the--this is a reanalysis of data that was submitted in the PMA. We realize that it makes some of the Panel members uncomfortable; however, it is fair to allow any sponsor to attempt to address issues that have arisen by providing a reanalysis of that information. We realize that it may put

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you in an uncomfortable state not seeing that data, but I think that that is a fair approach.

DR. MACSAI: Okay. So, then, can we go back--

DR. McCULLEY: Then we can go back to the previous slide, and that clarifies the point that this is data that had been previously submitted.

DR. PULIDO: No--can we go back one more prior to this one, because that was where we--right here.

[Slide.]

DR. PULIDO: Now, had this been a change in protocol?

DR. KREMER: No. It was an improvement in surgical technique, but not a discernible change in protocol.

MR. DAYTON: Both protocols had an allowance within them that said the surgeon may refine his technique, and that was done in this case. The centrization was improved, and we think these data demonstration that it was a worthwhile improvement in technique.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I have a problem with where we are going with this. We have been presented with two protocols, the IRB and the IDE, and I am willing to accept those two datasets as being complete and valid. What we are not being

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asked to evaluate, firstly, is an initial cohort of patients, what was called the Group 1 patients in the IRB protocol, as the sort of best case accountability; and now, we have sort of parceled out a group of fewer than--well, if you look at the 3-month or 6-month--fewer than 100 patients to look at the safety issue pertaining to refractive cylinder.

We are taking multiple looks at little pieces of data here, and I don't find that compelling--and possibly unsatisfactory as well.

DR. McCULLEY: Okay. I think your assessment of what is presented is certainly up to you. Their right to present it I think has been stated by the FDA. How we view their presentation is up to us.

DR. KREMER: I'd just--

DR. MACSAI: Dr. Macsai, is that--please do not speak unless you are called on. Dr. Macsai?

DR. MACSAI: Dr. Kremer, which surgeon's patients are we looking at here?

DR. KREMER: They are combined.

DR. MACSAI: So this is both yours and Dr. Pronesti's patients?

DR. KREMER: Yes, that's correct. It was not stratified by surgeon.

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DR. MACSAI: So this improvement was made 4 years after you initially began enrolling patients?

DR. KREMER: Yes.

DR. MACSAI: Could you just describe to me for my own interest--what was the difference?

DR. KREMER: Well, in the past, we had used the position of the pupil and the observation of the visual axis light reflex as the centration technique during the surgery for these patients. And we observed, though it took a while to figure it out, that these patients tend to drift during this procedures, and it is very difficult to observe that because of the presence of parallax. When you are looking at the pupil and the light reflex, there is parallax as you look through the cornea, so a slow, small drift is very difficult to detect.

So we came up with the idea that we would establish the location of the visual axis and the pupil and determine where and how we wanted the procedure centered at the beginning of the case--that is, prior to the cap being opened and while the patient had a good, easy view for a short period of time in the direction that we wanted.

We observed during that time period, and then we associated certain landmarks on the eye to other landmarks in the operative field as part of the operating microscope.

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And then, during the procedure, we still attempted to keep the treatment in the same place that we always attempted to keep it, so there was not any change from that standpoint. The only difference was that now, by using those landmarks, we could more accurately maintain that position, and that has shown not only in this data, but we have also observed it in the corneal topography.

DR. McCULLEY: If it's a burning question--we really need to start to address substantive issues, but one more informational question.

DR. MACSAI: One burning question. What was the rep rate of the laser firing during these versus other procedures?

DR. KREMER: Ten Hz. There was an entry in the submission which was misleading where it said 1 to 25 Hz. That should have been stated in the submission as 10 Hz. I won't waste time on why it was written that way.

DR. McCULLEY: Okay. Have you--yes?

MR. DAYTON: I would just like to put this in perspective, this issue of induced astigmatism with regard to spherical myopes, and I believe the Panel and the agency have provided guidance in the past for surface ablation for this subject.

Dr. Kremer, wanting to do the best that he can for

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his patients, has improved his technique, and the issue of centration I think is central to perhaps reducing astigmatism in one's procedure. However, that aside--and we presented that as an interesting analysis so that you could see that it progresses to be in favor of the patient--however, if you look at the data overall as we presented on Slide 46--Mike, can you move to Slide 46 please--

[Slide.]

--this subject is summarized and placed juxtaposed to the previously published guidance document on the subject of induced astigmatism greater than 2 diopters. Understand that this group of patients treated after May is a small subset of these patients. If you look at the line at the bottom, induced astigmatism greater than 2 diopters, you'll notice that these are spherical myopes, from which we have guidance, and you'll see in the IDE group, there were none with less than 7 diopters, which is what the guidance speaks to. If you include the "greater than" diopters, the "all eyes" next to it, .3 percent had greater than 2 diopters induced astigmatism.

In the IDE group, if you look at "less than 7 diopters," there were none; if you look at the "all eyes," including "greater than 7 diopters," you have .6.

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The guidance the Panel has previously accepted for spherical myopia is less than 5 percent. So we believe this is a bit of a moot point. We simply wanted to point out that it does make a difference how one concentrates, and that is an art, it is not a science.

DR. McCULLEY: All right. I think that what we are going to do at this point--Dr. Kremer, I am going to ask you to have a seat at the table, and if we could have the lights back on--we are going to now turn to the Panel and ask if the Panel has questions for sponsor at this point. What I am doing is we will now ask questions of them, rather than leaving them with the floor.

Dr. Sugar?

DR. SUGAR: Could you again address the issue of standardization of data retrieval--that is, from the patients. Was there a standardized viewing lane? Was there a standardized chart? And also, what about cycloplegia?

DR. KREMER: The examinations were done using Snellen eye charts with 20-foot lanes. They were required in each of the visits. All of the postoperative measurements were taken by doctors other than the surgeon. Cycloplegic refractions were performed at the preoperative visit but were used as a check on the manifest refraction.

In addition, when clinically indicated, for

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example, in patients where there was hyperopia, cycloplegic refractions were done to check those manifest refractions.

DR. McCULLEY: Maybe there have been too many legal proceedings on television. I think that was a nonresponsive response to the question as I understood the question. It was: Were the conditions standardized at all of the locations?

DR. KREMER: They were standardized to the extent that the doctors were all trained--trained and showed licensure--for being qualified eye doctors.

DR. McCULLEY: So the answer to that is no.

MS. LYDEN: Excuse me. This is Maureen Lyden. They also had all standardized case report forms.

DR. McCULLEY: Okay. The question is the examination environment, was it standardized, and their procedures for that, and I think you have given us your answer.

Are there other questions from the Panel for the sponsor?

Dr. Bullimore?

DR. BULLIMORE: Yes. I am unclear when I compare your Slide 19--and I don't need to see it on the screen--with Slide 27. According to Slide 19, 10 eyes were considered not eligible due to them undergoing hyperopic

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LASIK following, presumably, their primary procedure, yet we have I think a total of 44 on Slide 27. I am just curious why these are considered separate. Is there some sort of loss of acuity or degree of hyperopia that made you pull these two sets apart?

DR. MACSAI: Could you also, when you are answering that, explain to me if it's a total of 44, or if in fact the total is 54?

DR. McCULLEY: Is sponsor able to respond?

DR. KREMER: We may have to confer a little bit, but what may be the source here is that the N-tree is looking at the patients at the 6-month interval, and we have tried to provide more information where possible--Maureen, is that correct?

MS. LYDEN: Yes, that's correct, but on Slide 27, we're showing all the patients who were treated and what their enhancements were, whether they were myopic or hyperopic, and we do have those few that had a myopic with a larger ablation zone.

What is on Slide 19 is just showing those who are due for the 6-month visit and their status. So if there are eyes that have had a hyperopic enhancement and are not yet due for a 6-month interval, they wouldn't be appearing in Slide 19.

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DR. BULLIMORE: So all in all, thus far of your 2,400 patients, somewhere around 2 percent of them have needed hyperopic enhancement; correct?

MS. LYDEN: That's true.

DR. BULLIMORE: My question is perhaps directed at the agency or the administration as much as the sponsor on this one. Is the hyperopic protocol part of something that we are being asked to consider today, or is it just the myopic protocol?

DR. McCULLEY: Dr. Waxler?

DR. WAXLER: The hyperopia was not a part of this protocol, and therefore, there was some misunderstanding. There were some patients who were treated with the hyperopic procedure, so that's why--they really shouldn't be part of this PMA submission.

DR. McCULLEY: Does that clarify, Dr. Macsai?

DR. MACSAI: So, Dr. Waxler, are they under a separate IDE?

DR. ROSENTHAL: May I?

DR. McCULLEY: Dr. Rosenthal?

DR. ROSENTHAL: The patients should be started out myopic and should have been included in the analysis up to the point at which time they were inadvertently treated for hypermetropia. Does that make it clear?

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DR. McCULLEY: That was very nicely stated.

DR. MACSAI: Perfectly.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: Just another point of clarification. On Slide 42, where you talk about your complications, specifically, epithelium and interface, I'd just like to know what the definition of central versus peripheral is.

DR. McCULLEY: Dr. Kremer?

DR. KREMER: We refer to epithelium centrally meaning that it is individual axis and obstructing the vision and requiring removal.

DR. McCULLEY: You never had to remove the epithelium in the periphery?

DR. KREMER: Not in an isolated patch. If there was epithelium that started in the periphery but was connected to the more peripheral epithelium, it would then grow into the center and then be removed, but at that point, it would be classified as central.

DR. McCULLEY: So you didn't remove any while it was still on the periphery, before it went to the center, knowing it was going to go to the center. You waited until it got to the center.

DR. KREMER: We waited until it impacted the

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patient's vision, because if it stayed peripheral, as many of them do, percentage-wise, then we would not remove it.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: Just a question, since we have to compare this, I guess, to previous PRK data. There is about a 1-point-some-odd percent incidence of hingeless flaps, which are basically little corneal buttons. Did any of these patients need retreatment who had these hingeless flaps, and if so, what happened to the little button, number one. Number two, these are, as you said before, young patients who were active, and that was the reason why many of these didn't come back for follow-up. Well, likewise, these young patients are probably very active. If these hingeless flaps are easily dislodged to do secondary procedures, can they easily dislodge during sports activities, let's say?

DR. KREMER: No, they cannot. The incidence of the hingeless flaps was actually less than one percent. I am not aware of a case where a hingeless cap had a secondary procedure. However, if we were to approach such a case, the approach that would be taken would be to not entirely open the cap, but rather, still leave a hinged area, using the portion of the edge of the hinge as an anchor, leaving that part attached.

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DR. PULIDO: Thank you.

DR. KREMER: We did not see any clinical difference postoperatively with patients who had hingeless caps, and we have not seen any caps that have become dislodged postoperatively.

DR. McCULLEY: Dr. Sugar?

DR. SUGAR: To follow up on the preceding question, in the data you present, I think there were 4 patients with central epithelium. Were all those operated on to remove it?

DR. KREMER: Yes.

DR. SUGAR: And is that number 4 accurate?

MS. LYDEN: This is Maureen Lyden. I think there are 2 at 6 months. Those were the numbers we were reporting in the presentation were those that were at 6 months. There were more than that prior to that--a few more.

DR. SUGAR: Thank you.

DR. McCULLEY: Does the Panel have any additional pertinent questions for the sponsor?

Dr. Bullimore?

DR. BULLIMORE: One of the key issues identified by I guess all the reviewers is accountability, and I want to make sure I've got the numbers straight and that we're all happy with them before we excuse the sponsor.

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Working through the initial slide presentation, going to Slide 19, we had 1,402 eyes with 6-month follow-up out of a total of 2,121 evaluable. That, I guess, gives approximately two-thirds, or 66 percent; am I correct?

MS. LYDEN: Yes.

DR. McCULLEY: The response to that is "Yes."

DR. BULLIMORE: Okay. Now, since the initial review submission, there have been some other eyes out of the 2,000 available that have been examined, and then we could conceivably consider those as part of the accountability. What is that number of subjects that are in addition to those 1,402, or how many of those have subsequently been evaluated at a visit after 6 months?

DR. McCULLEY: Can you answer that?

MS. LYDEN: Yes. That answer is 301.

DR. BULLIMORE: So your total is 1,402 plus--what was the number you gave me--

DR. McCULLEY: That was in submitted data.

MS. LYDEN: In listing format in the PMA; that's correct.

DR. BULLIMORE: Is that consistent with what has been received by us?

DR. MACSAI: Let me just look.

DR. McCULLEY: Okay. Yes, Dr. Higginbotham?

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DR. HIGGINBOTHAM: I think I know the answer to this. Dr. Kremer, I know that the conditions were not standardized for your postoperative practitioners. Could you perhaps tell me if there was some attempt to define definitions for the various adverse reactions, particularly the infiltrates--I mean, did you have standardized charts or definitions--and then if you could also tell me how many practitioners were actually following your patients.

DR. KREMER: We had a course in which we would have the co-managers come and review this information. We did not standardize the description of infiltrates. In total, I don't know the exact number, but it is on the order of several hundred doctors who participated in this co-management process.

DR. HIGGINBOTHAM: "Several hundred," meaning less than 1,000 or more than--

DR. KREMER: Oh, yes, way less than 1,000.

DR. McCULLEY: Dr. Jurkus?

DR. JURKUS: I had a question about Slide Number 43, the patient symptoms bothersome after 6 months. Were this individual patients who reported each of the symptoms, or were there patients who had multiple symptoms, and if it were the multiple, do we have that type of breakdown?

DR. KREMER: It was not broken down to assess

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which patients described multiple of those symptoms. Clinically, we observed that the symptoms did tend to go together. In other words, a patient who had complaints of ghosting or double images would also have complaints of halos at night, for example.

DR. McCULLEY: Dr. Pulido?

DR. PULIDO: So, Dr. Kremer, you have this problem of accountability of patients coming back; you have also hundreds of doctors looking at these patients. Do we have the data on the follow-up per doctor--in other words, were there centers that had no follow-up whatsoever, doctors who had very little percent of reporting of the results of patients?

DR. KREMER: It's not stratified by the doctor.

DR. PULIDO: I see.

DR. McCULLEY: Okay. Dr. Macsai--let me remind the panel that we do have a series of questions posed by the FDA that they wish for us to respond to; we want to do it with the best information we can, and we will continue to query sponsor as long as we feel the need for additional information from them so that we can respond to the FDA.

Dr. Macsai?

DR. MACSAI: Dr. Kremer, did I hear you correctly--did you perform site visits at these co-managing

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physicians' offices, or did they come to your center for this orientation?

DR. KREMER: They came to ours.

DR. McCULLEY: Are there other questions?

[No response.]

DR. McCULLEY: Then, I'd like to thank the sponsor. Let me tell you that you will be asked under new law approximately two-thirds of the way through our deliberation, if I have some way of estimating when that's going to be, to return to the podium to address issues succinctly that have arisen during our discussion and then, once we have completed our discussion, prior to a recommendation being made, you will be asked to return again to--once again, succinctly--respond to issues that have arisen during the third part of our discussion, as will the FDA be asked to query us.

So thank you very much, and you may now leave the table.

We will need to go through--I think probably the best procedure for us to follow is I have two questions for clarification for the FDA, and then we will have open discussion on areas that we feel are important that are not going to be addressed in the nine questions posed to us by the FDA, and then we will start to work down the list of the

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questions. Once we have gone through the list of questions, after all other proceedings have taken place, we will call for a motion.

There are two questions that I have for the FDA that I am not certain about. A reference was made to a generic microkeratome. Does that imply generic, but approved otherwise microkeratome? What does that mean?

Nancy Brogdon is the Acting Director--that's probably not right--

MS. BROGDON: I am the Deputy Division Director, and I am in this chair today because Dr. Rosenthal has the role of the clinical reviewer.

DR. McCULLEY: Thank you.

MS. BROGDON: We have defined LASIK devices as systems that incorporate both the laser and the keratome. We would expect any sponsor to describe the keratome used during their study and to describe the keratome for which they are requesting approval as part of their system.

We have allowed sponsors to describe the specifications for their keratomes in their PMA submissions because it is assumed that after approval, other users of that system would be able to substitute other keratomes with identical specifications. I think that may be where the term "generic keratome" comes in; we presume that it was a

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single or more than one described keratome used during the study and that we know specifically what keratome would be used after approval if the PMA is approved.

It is fair game for the Panel to ask the specifications of the keratome if you feel that that is pertinent clinical information. If the PMA in this case were approved, the sponsor could use that keratome in the procedure after approval. They would not be able to market that keratome. Any keratome in use that is marketed in this country has to go through the premarket notification, 510(k) process, and I believe that the sponsor has been informed of this.

DR. McCULLEY: They reported using a specific microkeratome by name. That microkeratome is an approved microkeratome?

MS. BROGDON: I'm getting nods from staff, yes; that one apparently is an approved keratome.

DR. McCULLEY: All right.

MS. BROGDON: But again, if the PMA were approved the sponsor could use other keratomes with similar specifications.

DR. McCULLEY: Thank you for that clarification.

My second question is my understanding relative to PMAs is that they would be based on IDE data as the

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principal source of data, that it is acceptable to have as supplemental, supportive, clarifying data international data, or in this case, IRB data. Is that an accurate statement?

MS. BROGDON: I am not sure I can give you a yes or no on that one, but I have several statements that I could make that I believe are true, and I would ask Dr. Waxler to correct me if I am off-base on any of this.

First of all, a PMA must contain all available data, so that if there were data gathered internationally, or animal studies or whatever, those would need to be submitted in the PMA. The PMA cohort on which the PMA is really based, however it is constituted, must consist of valid scientific evidence, and so you would need to judge whether the PMA cohort or cohorts here contain valid scientific evidence. It is up to the sponsor to propose what they believe are the appropriate cohorts in the submission. It is up to the Panel to make any recommendation you wish about the validity of the data in the cohorts.

This is an atypical situation we have here. The situation hasn't arisen very frequently that there is such a body of data that have been collected before an IDE approval. That is why you are faced with a large cohort of

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U.S. data, and that's what the sponsor has chosen to call their IRB cohort.

DR. WAXLER: Can I add, Nancy?

DR. McCULLEY: Please.

DR. WAXLER: I am Morris Waxler, and I would only add--I agree exactly with what Nancy said--that could be solely based on foreign data. It's really--

DR. McCULLEY: It could be?

DR. WAXLER: It could be. In this case, it could be solely based on the IRB data; it could be. It is really a question of how you define valid scientific evidence; it's a judgment call on your part in terms of whether that data shows a reasonable assurance of safety and effectiveness.

DR. McCULLEY: Thank you. I think that response helps, both of your responses help a great deal.

Nancy?

MS. BROGDON: I have one more thing I would like to say. It is important for the agency and for the sponsor, too, to know what you believe about these two different cohorts, because it will need to be clear at the end of this process today on which cohort you are basing your recommendations to us. We'll need to know that, and any work that we do later in the agency will need to be applied to one cohort or the other or both of them. So we will need

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to have your specific recommendations.

DR. McCULLEY: Yes. Well, I guess I had misassumed. My assumption would have been that data supporting a PMA would have to have a substantial cohort that was an IDE gathered data, and that the other data could be supplementary. But what you are telling me is that that is not the case, and I think that's important for us to understand. Okay. I am now un-ignorant about that.

Yes?

DR. ROSENTHAL: Your assumption is correct that it is based on the fact that we can accept foreign data for PMAs, and if you would feel that foreign data would not be an IDE, then your assumption is correct.

DR. McCULLEY: No. My assumption was incorrect--that it had to have a core IDE data.

DR. ROSENTHAL: Your assumption was incorrect, that we can accept data that--if we can accept foreign data--

DR. McCULLEY: In toto.

DR. ROSENTHAL: Right.

DR. McCULLEY: Okay. I think that's clear. Thank you for the clarification.

Where we are now in our deliberations is are there discussions that we need to carry on, or should we now go to

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answering the questions that have been posed to us by the
FDA?

Dr. Bullimore?

DR. BULLIMORE: I think answering the questions is
a good idea but with the provision that we could go back and
revisit some of the independent issues raised by Drs. Sugar
and Macsai after we've dealt with the questions.

MS. THORNTON: If we are going to go ahead now
with Panel deliberations, I'd like to ask the FDA staff
please to take their seats to the side of the table. Thank
you.

DR. McCULLEY: Sorry--I wouldn't desert too fast,
guys--is that indeed what we want to do, is start with the
questions?

Dr. Higginbotham?

DR. HIGGINBOTHAM: One of my concerns, based on
the previous discussion that we just had, I may have some
additional questions for the sponsor in terms of the
subgroup if there were differences, for instance, in the way
the patients were followed; if there were no differences,
then it is probably not a valid line of inquiry, but if we
can actually filet this data in such a way that we can
actually determine if there were cohorts within the data
that had better accountability, that might be helpful.

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Maybe that question requires some discussion.

DR. MACSAI: From my detailed review, Dr. Higginbotham, of the data submitted, there was no segregation of the data postoperatively by examiner, and I was just informed by Dr. Kremer that there was no site inspection of the places that those examinations took place.

Therefore, we have not received the data you are requesting.

DR. McCULLEY: Okay. Shall we begin with the questions? Okay.

We have nine questions, and we'll go down them in order. Does the FDA have projections of these, or will they just be read?

DR. MACSAI: We have them.

DR. McCULLEY: I know, but the audience does not.

Okay. I will start reading. The first question relates to accountability. I will read the question as it was initially posed.

"The accountability in this PMA is between 65 and 85 percent for both cohorts. Previous Panel recommendations have required accountability to be 90 percent. Do you believe the large number of subjects reported in this PMA as well as the line item information concerning UCVA and BSCVA on the last reported visit of those who were not eligible or

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those who missed visit (Addendum) allowed one to make a decision on safety and efficacy at the reported level of accountability?"

Now, questions can be answered "Yes," "No," and with all sorts of clarifications, but let's try to work toward a definitive answer.

Let me ask Dr. Macsai, who is primary reviewer, and then Dr. Sugar and other Panel members' input.

What would be your response to that question, Dr. Macsai?

DR. MACSAI: My response is that there is a significant problem with accountability with this application. Even if you look at the most recent submission from the sponsor in Section 18 of the IRB data, the IDE protocol, looking at all eyes treated, only reports 75.8 percent accountability at 6 months, and that's just kind of across-the-board at the 1-, 3-, and 6-month visits. So the accountability is very low, and in an IDE, I would expect it to be higher.

DR. McCULLEY: So your response would be that one would not be able to make a decision on safety and efficacy at the reported level of accountability?

DR. MACSAI: Yes; my response would be no.

DR. McCULLEY: Dr. Sugar?

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DR. SUGAR: The reported level of accountability, I get 73 percent and 77 percent for the IDE and the IRB protocols, respectively, and this doesn't meet the 90 percent guideline. I think that the way the numbers have been reworked and resubmitted to us, the accountability is borderline, and I would still say "No," but I am approaching the fence.

DR. McCULLEY: Okay. Other comments?

DR. MACSAI: Can I recommend?

DR. McCULLEY: Yes. I want to give everyone a chance to speak, but I certainly will give you a chance to speak again. Dr. Macsai?

DR. MACSAI: I also want to make a comment about that. No--if the data had been collected in standardized fashion and standardized situations, if I were more confident in what I was reviewing the accountability might be high enough due to the size of the study that I would feel differently. But there is a tremendous amount of confusion in my mind about these patients--who followed them, what guidelines, where were they followed, how were the measurements made, were there site visits, et cetera. So it decreases my level of confidence on that which has been presented.

DR. McCULLEY: Okay. Other comments? Yes?

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DR. YAROSS: I just want to make sure that everyone with the Panel and the FDA is aware of a concern on the part of some members of industry that there be a single standard of accountability and a single set of standards for both commercial and physician sponsors.

Thank you.

DR. McCULLEY: My understanding is that there is no differentiation based on source of sponsor, and there are guidelines that are set, but as with everything, what goes with it is the implication of a guideline. And we have set it at 90 percent.

DR. BULLIMORE: I really do share concerns about the accountability. The fact that if we consider one small sub-cohort to have adequate accountability doesn't make me any happier, because one would have thought that as part of an IDE protocol, they would have been trying as hard, if not harder, to keep hold of these patients than they did in their initial studies.

I don't like the idea of taking 2,000 patients and looking for the best quartile or 10th percentile in terms of either outcome, safety measures, or accountability. We certainly wouldn't do that in other settings, and I don't think we should do it here.

DR. McCULLEY: Okay. Well-put.

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Dr. Pulido?

DR. PULIDO: Mr. Chairman, since it seems to me that we have a great problem with the accountability, and we don't want to lower the threshold of accountability, and since all of the questions flow from this one, if we can't get past this one, I would like to vote for disapproval at this point.

DR. McCULLEY: We are advisory to the FDA, and that is our role, so I would ask the FDA that if that happens, be thinking about if our suggestion is that the answer is "No" here, do you want us to address the other questions or not.

DR. WAXLER: Absolutely

DR. ROSENTHAL: Yes.

DR. McCULLEY: And the answer to that is yes--Dr. Waxler, Dr. Rosenthal.

DR. MACSAI: There is a motion on the floor--no?

DR. McCULLEY: No, there is no motion on the floor. We're talking.

DR. MACSAI: Okay.

DR. McCULLEY: I thought I had indicated that we will address all of the other questions that the FDA requests that we do.

Are there any other comments about accountability?

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There has been no dissenting view stated, and I think that if there is a dissenting view, certainly, one needs to speak up in that regard.

[No response.]

DR. McCULLEY: Then, shall I take a motion--I guess we don't do that on each question. We have our answer. The answer from the Panel to Question Number 1 would be that we do not feel comfortable with the accountability to allow us to assess safety and efficacy. That would be our response to that question, and I guess we don't do this by motion and so forth, so that is our consensus.

Question Number 2. "Stability. The stability results in this PMA was based on 139 patients in the IDE cohort (n = 1,360) and 304 subjects in the IRB cohort (n = 1,140). These numbers are a small fraction of the total treated and represent those subjects who were examined at all 4 postoperative visits. Is it reasonable to accept the stability percentages based on the numbers reported?"

Dr. Sugar?

DR. SUGAR: I don't believe there is adequate evidence of stability.

DR. McCULLEY: Okay. Dr. Bullimore?

DR. BULLIMORE: I think the numbers come up to the

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required guidelines in the patients that have been followed. I'd like to point out that I was not satisfied with the answers I received earlier when I was comparing numerators and denominators and different cuts of the data.

My concern with the stability issue arises out of the accountability issue.

DR. McCULLEY: Okay. Dr. Macsai, would you like to add to that, or not?

DR. MACSAI: I concur with Dr. Sugar.

DR. McCULLEY: Okay. Are there other views that any Panel member would like to state?

[No response.]

DR. McCULLEY: So, then, our response would be that we aren't comfortable with the stability percentages based on the numbers reported.

Question Number 3. "Increase in cylinder in eyes treated for spherical myopia: The increase in cylinder which occurs in the eyes treated for spherical myopia ranges from approximately 50 percent who show an increase of equal to or greater than 0.25 diopter to between 2 and 7 percent who show an increase in cylinder of equal to or greater than 1.5 diopters. Is this of concern?"

Dr. Sugar?

DR. SUGAR: It's of great concern. The data

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presented for after May 1st, which I don't think helps us, shows obviously that the investigators were concerned as well. And there are only 11 patients reported with 6-month follow-up with whatever their change in protocol was. I think we have to base our judgments on the information presented to us, and the induced cylinder is unacceptable.

DR. McCULLEY: Other comments?

Dr. Macsai?

DR. MACSAI: I would concur with Dr. Sugar, and I would also express the concern that the sponsor stated that some of the retreatments were astigmatic keratotomy, and whether those were performed on patients who were originally spherical and had that done for induced astigmatism would be an important issue to sort out.

DR. McCULLEY: Are there other views, especially to the contrary?

Dr. Bullimore?

DR. BULLIMORE: Well, some of my best friend are astigmats, and inducing astigmatism in someone in itself doesn't present too big an issue; I mean, it's almost an efficacy issue as much as a safety issue.

DR. McCULLEY: It depends on the degree of astigmatism induced.

DR. BULLIMORE: Absolutely. But the line that has

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been previously drawn in the sand by this and other panels is 2 diopters, and I will accept that, on the data that we have had presented, the sponsor meets the standard. I think, however, it is prudent that some attempt is made to understand why this astigmatism is getting induced, and that in itself makes it unacceptable. There is no analysis of topography; we don't know whether it is the flap, the ablation zone, where there is some wobbliness in the laser beam that's just randomly inducing this, or if it's just plain old noise.

So I'd like to note that they have reached the guideline standard--

DR. McCULLEY: Relative to 2 diopters.

DR. BULLIMORE: Sorry?

DR. McCULLEY: Relative to 2 diopters.

DR. BULLIMORE: Relative to 2 diopters, which is the only guideline that we have, but there is some residual concern.

DR. McCULLEY: Okay. I think that the guidelines are of use where we have a guideline, but that doesn't mean that we have to close our minds to other issues that aren't addressed. And in looking at the numbers, if I can read my scribbling, we had 42 to 50 percent of induced astigmatism, but approximately 10 percent of that was 0.25 diopter, and

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10 percent was 0.50 diopter.

I agree with you that I don't worry that much at that level, but when it starts to get up to a diopter and more induced, whether we have a guideline or not, that does raise concern for me.

Dr. Sugar?

DR. SUGAR: Dr. Bullimore mentioned that some of his best friends are astigmats. All the patients in here were astigmats or myopes, and I have similar kinds of friends. But if the goal is to eliminate either your friends or the astigmatism and the myopia, then unless we have data that shows that those people with induced myopia had acuities that were better than 20/40 or better than 20/20 uncorrected, we are assuming that those were failures in the sense that their need for spectacles was not eliminated.

DR. McCULLEY: I think that that is a very good point, and to restate it as I understand it, that is a concern with this degree of induction of cylinder, and it would be of use to have a separate analysis of those patients to determine whether there was harm or whether it made no difference to them.

DR. BULLIMORE: I guess that what I really wanted to point out is that this is not necessarily a safety issue, that it sort of borders on being an efficacy issue. This

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was Dr. Bullimore, who was unrecognized by the chair and apologizes.

DR. McCULLEY: Don't do it again. Dr. Macsai?

[Laughter.]

DR. MACSAI: In follow-up to Dr. Sugar's and Dr. Bullimore's comments, I would also think that in the subpopulation, it would be very important to know their cycloplegic refraction. You know, if there spherical equivalent is plus 0.50 because they have one diopter, the plain old plus one, they're working hard to get over that, and when they hit 40 or whatever, it is going to be a problem for these patients.

DR. McCULLEY: Yes. I think you have made that point before and effectively again, and I think that that needs to be remembered.

So the answer, then, to Number 3, the increase in cylinder, is this a concern, the answer is "Yes."

Question Number 4. "Stability of cylindrical correction: The data on stability of cylindrical correction based on manifest refraction in subjects treated for myopic astigmatism indicates a drop in the percent who change by equal to or less than one diopter between 6 and 12 months as compared to previous intervals. This was observed in both protocols. Does this indicate that the stability of the

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resultant cylindrical correction will continue to decline after 12 months, and if so, is further follow-up required either before or after PMA decision?"

Dr. Macsai?

DR. MACSAI: I separate this Question Number 4 into two answers. We don't know if this indicates that the stability of the resultant cylindrical correction will continue to decline after 12 months because we don't have that data. What we have is simply a trend, and because we have a trend, we need to follow it.

Therefore, my response to the second part regarding follow-up is "Yes."

DR. McCULLEY: So it is "Don't know" and "Yes" is what you are suggesting.

Are there other comments from anyone, either direction? Please, if you are not in concurrence with what is being stated, your silence implies concurrence, so please speak up if you do not concur.

Dr. Bullimore?

DR. BULLIMORE: Can someone just refer me to the data table that Dr. Rosenthal's statement is based on?

DR. McCULLEY: That was presented--you remember it; you just want to see it again.

DR. BULLIMORE: I want to see it again. I am just

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trying to find it.

DR. McCULLEY: Dr. Rosenthal, would you mind letting someone else put up one of your overheads?

DR. ROSENTHAL: You want stability of cylindrical correction; is that correct?

DR. McCULLEY: It is Question Number 4.

While we are doing that, let me raise a question I have that we are skirting around. We have indicated in the past that if the posterior 250 microns of the cornea is not invaded, that we are comfortable relative to endothelial health. There have been statements made as well that with 250 microns of undisturbed posterior stroma, that one expects to have anatomical stability or structural integrity of the cornea. Is that now dropped to 200, or is 200 to 250 a questionable zone? What is the status of this? I think we need to have some understanding, because this protocol allowed down to 200, and we didn't hear any additional endothelial data. To the best of my knowledge, we don't know about structural integrity when one goes down to 200, one way or the other. So is 200 an acceptable zone, or if it isn't, do other studies not need to be done to ensure that that 250 drop to 200 is okay?

DR. SUGAR: We discussed this at the guideline meeting, and I don't know that we really resolved it--did

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we, Morris?

DR. ROSENTHAL: No.

DR. SUGAR: Scot McRea [ph] presented suggestive data that 200 was reasonable; we never--I don't think--made any specific decision.

DR. McCULLEY: I think there are two concerns that I am aware of. One is endothelium, and Scott, I think, had some data on endothelium; the other is anatomical integrity, structural integrity. I mean, some of these instability issues--and that's what brought it to mind here, that apparent increasing instability, maybe--could that be related to invasion deeper than 250, or not leaving a full 250 microns behind.

Dr. Macsai?

DR. MACSAI: I don't have the answer.

DR. McCULLEY: I think we have a comfortable level down to 250. Anything that goes below 250, I think raises additional safety and possibly efficacy issues. So I think that that needs to be clear and made clear to the sponsors.

Nancy?

MS. BROGDON: We are interested in this discussion, because it's part of the request in the PMA, so we'd like your input.

DR. McCULLEY: Well, I think our response--I mean,

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it wasn't one of the questions here--but the response would be that we're not certain below 250.

DR. SUGAR: Well, the response would also be that we need more data from the sponsors.

DR. McCULLEY: Right, right. It would have to be substantiated that it can't just be--I mean, 250 would be accepted as a watermark. Anything less than that would need supporting data.

DR. SUGAR: Since we were not presented data on depths of ablations anywhere in the PMA until today, and again, we were just told how many microns per laser--we would need to get data on stability of astigmatism stratified by either degree of myopia or depth of ablation, assuming that those are the same.

DR. McCULLEY: Well-stated.

Now, we were looking for something for you. We have found it.

Dr. Bullimore?

DR. BULLIMORE: We have found it. This table doesn't make sense, and I'll just go on the record as saying as much. If you compare the mean differences across those three intervals, they are identical. If you look at the standard deviations, they are decreasing. Intuitively, one would expect the stability, based on the number of patients,

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changing by one diopter or less to go up. However, if you look at that last top right-hand data cell, the proportion is 166 out of 278. That is inconsistent with the mean and standard deviation below that. One would expect the stability to be better based on the mean and standard deviation. So there has been, I can only assume, an error made in one of those cells that needs to be remedied, looked into, probably at some later date. But based on the top right-hand number, the stability is unsatisfactory.

DR. McCULLEY: Okay. I think Dr. Macsai's response on "Does this indicate that the stability of the resultant cylindrical correction will continue to decline after 12 months?" was that we really don't know. And do we need further follow-up? Yes. I think if we just answer the question in that context, her proposed answer is acceptable.

DR. BULLIMORE: I think you should define--that table is inconsistent, and someone needs to figure out what the inconsistency is, and that can be construed as follow-up, but I don't want--if it's really a mathematical error--

DR. McCULLEY: Okay. Good point.

DR. BULLIMORE: --we don't need 2-year data.

DR. McCULLEY: Good, good point. So there appears to be some problem with the data, and if the data hold to

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suggest this trend, we don't know; and yes, if the data end up not showing this trend, then this question would be stricken.

Okay. Question Number 5. "Shift in cylinder axis: In the astigmatic myopes approximately 50 percent in the IRB cohort and 33 percent in the IDE cohort demonstrated an absolute shift in axis at all residual cylindrical magnitudes. Is this of concern, and if so, how should this be addressed in the labeling? Would any further studies be indicated?"

Responses? Dr. Sugar?

DR. SUGAR: It's a concern. How important it is, I am not sure. And if you add it to the other issues with cylinder, it fits in the same category, but in terms of clinical significance of this, I am not certain.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I'll agree with Dr. Sugar. The clinical significance of a change in cylinder axis after refractive surgery procedure depends so much on the change in cylinder power, it's very difficult to interpret alone. For example, you could have a patient who is started with--let's make it neutral--a 2-diopter cylinder at axis 90, and postoperatively ends up with a 0.25 cylinder axis 180. That's a huge shift in cylinder, but that could be

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considered a great outcome.

Now, the sponsor has stratified their data accordingly, and clearly, there are some cells within that stratification where there has been a group or a single bad outcome, and I saw Dr. Sugar and Dr. Macsai circling those. I think that alone, we should not consider shift in cylinder axis as a cause for concern; I think we need to consider it in terms of some other context.

DR. McCULLEY: Axis shift and magnitude.

DR. BULLIMORE: Rather than considering the shift in axis, we need to consider two things--well, I may add more to that--we need to consider the induced change, that is, the post minus the pre cylinder and axis; we need to subtract those two by vector methods and consider how close the change in power and change in axis are to that which was intended. And I have already discussed this with FDA staff, and that is there sort of proposed template, I believe, in future considerations.

DR. McCULLEY: May I ask FDA if Dr. Bullimore's response to that is sufficient in lieu of an answer to Number 5?

MS. BROGDON: I would have to ask Dr. Waxler.

[Ms. Brogdon and Dr. Waxler conferring.]

DR. McCULLEY: We are conferring once again.

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DR. WAXLER: The referees have consulted again.
Yes, that is a reasonable interpretation of our discussion.

DR. McCULLEY: Thank you.

Question Number 6--and I will let sponsor be aware that after this question, I will ask if you wish to return to the podium to make succinct statements relative to discussions that have taken place up to this point, and then we will have three more questions we will address, and you will be offered another opportunity after that.

This is completely new territory for us. I would think that this is an opportunity for sponsor to make statements, not to present data, not for us to query sponsor; it does not reopen the floor. Fair enough? Okay.

Number 6. "Retreatments and labeling: The sponsor presents data on retreatments as two or more LASIK treatments. With regard to labeling concerning retreatment, should we ask the sponsor to present a breakout on subjects who have undergone higher numbers of retreatments?"

Dr. Sugar?

DR. SUGAR: I think that was dealt with in the presentation this morning, that there weren't any people who had more than two retreatments. Certainly, the labeling should include the percentage of patients that required retreatments or enhancements or however you describe them.

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DR. McCULLEY: Dr. Macsai?

DR. MACSAI: I would also stress that in my analysis, the patients who required two or more LASIK did have a worse outcome. For example, in looking at best spectacle corrected visual acuity less than 20/25 when they began with 20/20, in spherical myopes who required two or more LASIKS, that was as high as 11.8 percent in the IRB group.

DR. McCULLEY: Okay, so--

DR. MACSAI: So that's saying that almost 12 percent of the spherical myopes who had two LASIK ended up with best spectacle corrected visual acuity worse than 20/25 when before surgery, they had 20/20.

DR. McCULLEY: Okay. So our response to that would be that labeling needs to address the percentage of patients requiring retreatment and the comment that patients requiring retreatment have a less good ultimate outcome than those requiring only one treatment.

Is there concurrence on that?

DR. BULLIMORE: I agree.

DR. McCULLEY: Is there disagreement?

[No response.]

DR. McCULLEY: Again, silence is concurrence, so I have to count on you to speak up. We need all views stated.

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Okay. This is two-thirds of the way through the questions that have been posed to us. At this point, I would like to offer sponsor the opportunity to return to the podium to make a statement. One person to the podium, please.

The chair recognizes Dr. Kremer.

DR. KREMER: Thank you.

When I was in elementary school, I read about how some inventors had been before their time. I never understood what that meant. I do now. It never made sense to me that if a person did something better, people wouldn't accept it--if it was better, it should be accepted.

I will be very succinct in going through these things, and I will try to respond to them in about the order that they have come up.

This study was driven by an intent to take care of patients in the best way possible before this technology was available. One of the things you asked about was the keratome. All of these cases were done with an automated Ruiz chyron microkeratome, which was and is FDA-approved.

This study was specifically for the treatment of primary myopia with and without astigmatism. Therefore, it did not include cases of patients who had had other types of refractive surgery such as RK or keratomileusis. I think

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that's a very appropriate question, and I want to emphasize that this was specifically for primary treatment.

With regard to stability of refraction, regarding spherical correction, we did that intentionally to look at cases that had been present for every, single one of the postop visits. And we know from looking at other studies that even though that was a smaller percentage of the overall population, that has also been the case in other studies. It is hard to get these young, mobile patients to come in for every, single visit, and yet in order to be a valid analysis of stability, you need the measurements from each of those visits.

We have also acknowledged that in the initial submission, the stability for cylindrical correction should have been done differently, and we have attempted to demonstrate that and will be happy to provide more detail if you wish on why we feel that the stability both for spherical and cylindrical has in fact been shown to be stable.

I am not sure--I'm going to jump around a little--why it was noted in the discussion that the enhancement rate was 49 percent. It was much less than that. It was about 16-point-some-odd percent in the IRB and about 5 percent in the IDE cohort.

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Of interest, the study that was referenced in the earlier discussion to which you were comparing our study only had an accountability of 32 percent, so on the one hand, it seems like there are some instances where a less than 95 percent accountability is acceptable, and in others, it is not. In a second study that was referenced today, there were only 10 people in the study.

So we think that the reason why accountability is important is because you want to be sure that there is no bias in the conclusion that you draw from a study. That's the reason for accountability. It is not because you need a specific number, but rather because you want to avoid bias. And we think we have shown that this was not biased in a couple of different ways--one, by showing that the outcomes of safety and efficacy were the same for those in the 6-month study as well as the ones that were not.

Although there were not site visits made at the co-managing offices, we feel that it is reasonable to expect that a licensed optometrist and licensed ophthalmologist is fully capable of taking manifest refractions and visual acuity measurements in a somewhat standardized fashion. And there are other scientific studies where standardization may vary from what you might consider an optimum. And there are other scientific studies--there is a cardiac study, for

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example, that draws on many thousands of patients, and it's not standardized in any way, but because the sample size is so large, they can still draw a valid, nonbiased conclusion, as I believe we have done with our study.

There was a second surgeon--we didn't get to show the slide, but I'll just summarize--where the outcomes were essentially the same, with the exception of there being a higher percentage of cases within plus or minus 0.50 and plus or minus one diopter, and this was consistent with the fact that the second surgeon had a higher percentage of cases that started out with less than 7 diopters of correction. And there was a slightly higher incidence of aborted procedures.

DR. McCULLEY: Just to remind you, you will be invited back again; but continue if you wish.

DR. KREMER: Okay, and I will be brief. With regard to the 200 micron limitation from the posterior surface of the cornea, this was a guideline that was presented to us. I think the comments are well-taken in terms of raising certain questions in that regard.

Please keep in mind that it is an extremely small percentage of cases, and in fact, since we limited our application to 15 diopters, it may be that there were none or, if so, very few that were anywhere close to 200 microns

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from the posterior surface. Our calculation for that depth uses the Monolin [ph] formula and adds the 160 microns for the cap.

So if there is interest in more discussion there, I'll be happy to give other input on that.

The shift in axis that we saw in some patients beyond 30 degrees, we are not certain of the mechanism of that, but there may be a little bit of the compass effect--when you get to the North Pole, the compass needle can sort of go in any direction--and that may be playing a role with these cases. In any event, we did not appreciate an adverse clinical impact from that shift.

Finally, I indicated earlier that we did study all of the cases in this series, so although it may not show a higher "percentage accountability" at the 6-month interval, all of the eyes have been studied. And we took particular interest to look at patients who had been noted as having a decrease of more than 2 lines of visual acuity or who had worse than 20/40 best corrected acuity, and interestingly enough--and part of the reason I think it is important to emphasize this is because of the concern that was voiced about the stats not being as good after enhancement as for procedures that did not have enhancement--but still, when you look at the entire group, what we found was that when we

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look at their final outcomes, there are patients who had decreases in best corrected acuity, maybe at the 3-month or 6-month level, but who then improved further. So that in each of the studies, in each cohort, there were very, very few, on the order of one or two per cohort, where there was a final outcome, where there was a decrease like that that was not related to some other mechanism. In other words, don't forget, we did not subtract out the patients who had some cataract formation and so forth. So I think that we have demonstrated a very high level of safety and efficacy with these procedures.

If I may, I think Mike Dayton would like to make a couple of further comments about the accountability.

DR. McCULLEY: Mr. Dayton?

MR. DAYTON: Thank you.

First of all, I'd like to address a couple of issues, accountability, and one that we didn't talk about was stability of manifest refraction. We have talked about stability of cylinder, but we didn't get to present our refractive, so I think it's important that we look into that.

First, let me speak to accountability--

DR. McCULLEY: Before you do that, let me just be sure that we are clear. Again, I'm trying to be just as

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fair and appropriate in this as I can. You are asked at this point to make statements--and this may be exactly what you are planning to do--related to issues that we have brought up in our discussion to this point--not to present any additional data.

MR. DAYTON: That is correct.

DR. McCULLEY: Okay.

MR. DAYTON: Concerning accountability, first of all, I would like to point out that there is a difference between accountability and follow-up. The follow-up in this study is very good with regard to eyes and knowing what they were doing when they were last seen and after the 6-month visit; we have accounted for 100 percent of those eyes.

Accountability is really more speaking to those data that you are looking at at 6 months and, of those data you are looking at, are they valid and are they reliable. Previously, the FDA and the Panel have said and set the benchmark that for an acceptable premarket approval application to achieve an accountability that is valid and reliable, you have stated that you want to see between 300 and 400 eyes at 6 months, of which you required a 90 percent accountability.

That would mean that you were expecting to see a PMA with 6-month follow-up with 260 to 370 eyes. In the

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Kremer Laser Eye application at 6 months, you are seeing over 1,400 eyes. That's the first point, because that speaks to are the summary statistics that you have before you robust enough, that is, are the summary statistics reliable, and we think that when you have 1,400 as opposed to 370, that in fact you could say those are fairly robust numbers.

Taking into consideration that and the agency's prior interest in 370 eyes at 6 months, when one begins to stratify across low and high diopters, with and without astigmatism, suddenly, your n's drop. How can you make a decision in those small n's with those few eyes?

In addition, when you are speaking about bias--that's the second issue of whether the data are valid--one, is it reliable--we have answered that. The other one, are they biased in any way. And the question really is are they negatively biased. I think that what we attempted to do was present to you the new table, where we broke out Table 1(a), and we looked at patients who missed their 6-month accountability visit but were followed, and we know their final status. And we presented those safety and efficacy variables because that's how we determine whether or not these data meet a benchmark.

We have pointed out that patients who did not make

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their 6-month visit but were seen prior to that had safety and efficacy outcomes as good as and perhaps maybe even better than the 6-month patients. Likewise, patients who missed their 6-month interval but were seen subsequently at 12 months were likewise doing better than or certainly as good as patients who came for the 6-month accountability visit.

What that would mean is there is no negative bias. We know about those patient eyes; we know how they are doing on safety and efficacy variables.

So when we speak of accountability, we need to think about it as a statistician and think about it in terms of reliability and validity of the data being presented, not some hard and fast rule that we want to see 300 eyes at 90 percent.

The second issue I'd like to talk about is stability of manifest refraction, and I am a little disappointed that we didn't get to that, because I think it is very important for us to understand what we are talking about here in comparing apples to oranges.

DR. McCULLEY: I think this is where I had a concern before about--and we had these proceedings, and you have your time initially to present and so forth--that it really is not fair to open the floor to you to present

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additional new data.

MR. DAYTON: I would not be presenting new additional data.

DR. McCULLEY: Well, presenting data--I mean, we had our six questions that we have responded to, and for you to address our response if you have anything to say relative to that. If you want to make an argument at this point--for lack of a better word--relative to the stability of manifest refraction, I am not certain that that is appropriate to the proceedings here, but I could be wrong, and I need guidance.

Am I correct, or--

MS. THORNTON: This time is for clarification, for the industry to come forward and clarify for the Panel any areas that they think we need clarification on that we have already discussed.

DR. McCULLEY: Okay. Again, we are on new ground here.

MR. DAYTON: Okay. I appreciate that, sir, and that's exactly what I'm trying to do--

DR. McCULLEY: Okay.

MR. DAYTON: --is to clarify from what I was hearing. And we didn't get to present stability of manifest refraction, so I think it is important that we tell you where we believe your interpretation may be off from what

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the data--at least, as we read the data.

DR. McCULLEY: Okay. I am not certain about the propriety of this, but if you will do it in a reasonable length of time--

MR. DAYTON: I'll be brief.

DR. McCULLEY: --being uncertain, I will allow it.

MR. DAYTON: I'll be brief.

The proportion of eyes that are seen over a stability analysis has previously been determined as eyes that are available at all intervals, and that one determines stability based upon whether or not it has shifted greater than or less than a diopter from two consecutive intervals. But for the analysis to be appropriate, you need to include subjects who have been at all intervals.

We thought that we were being extremely forthcoming with the panel by, for the first time, presenting all four intervals, which made our accountability of 443 eyes out of 1,580 at 28 percent--that is, 28 percent of the eyes were seen at the stability manifest refraction interval. And that is, for those who are interested, on pages 203 and 206 of the PMA.

What we wanted to do was compare to what had been previously presented to the Panel, which was three intervals--and I might add that the prior approval was based

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on 147 eyes out of 480, which made it 31 percent of subjects available, with three intervals. So what we did, in order to compare ourselves with the prior standard, was base it on three intervals, and when we did that, and what we were trying to present in Table 2.2 of the new information and Table 2.2.1(a)--sorry, let's just stick with 2.2(a)--when we compared the three consecutive intervals as prior sponsor, the number of eyes seen was 43 percent, exceeding the prior sponsor's number of eyes seen. And again, the stability is quite high.

So I just want to rebut that we had a low accountability or a low number of eyes that were seen in an interval. We simply presented at all intervals, where prior sponsors only presented three consecutive intervals.

DR. McCULLEY: Okay, thank you.

I think what we will do now is return to the three questions, and at least what I have in mind, unless you guys think otherwise, will be that after those three responses that we have, we will invite sponsor back, and then I will ask the Panel if their response to any of the questions that we have addressed--if you would like to change them based on the deliberations that include the response from sponsor. And we will also give the FDA a chance to ask if they have any further questions.

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Does that sound like a reasonable approach? The alternative would be to address the previous six questions, and I think it is better to do it when we are all the way through. Okay.

Question Number 7. "Indications: The sponsors request treatment with the device in a range between minus 1.00 and minus 15.00 of spherical myopia. Is this justified, and if not, should there be a different upper limit?"

There was also an issue that was brought up about the range of astigmatism, and the comment that I heard if I am quoting it correctly is that there were very few patients above minus 12 spherical and very few above 3 astigmatism.

Dr. Macsai, would you like to respond to that question? I think it should include astigmatism as well as sphere?

DR. MACSAI: There were few patients treated over minus 12 diopters of myopia, and 95 percent of eyes had less than 3 diopters of cylinder. I would be comfortable with the 12 and 3 cut-off. I can't, on 5 percent, really evaluate for between 3 and 4 and over 12. It's very difficult with such low numbers.

DR. McCULLEY: Other opinions?

Dr. Pulido, do you agree, disagree?

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DR. PULIDO: I agree.

DR. McCULLEY: Any other opinions?

[No response.]

DR. McCULLEY: So the opinion would be that the range would be minus 1 to minus 12, and 3 or less diopters of astigmatism.

Dr. Bullimore, you are leaning toward the mike?

DR. BULLIMORE: Minus 10.

DR. McCULLEY: You say minus 10?

DR. BULLIMORE: Yes.

DR. McCULLEY: Based on?

DR. BULLIMORE: Table 6.4.2.

DR. McCULLEY: What is it you are seeing on that table?

DR. BULLIMORE: We are dealing with a distribution with a long and slope in tail, and I just choose to make my cut point at a slightly more conservative point than Dr. Macsai.

DR. McCULLEY: Can you offer more statements so the Panel can decide?

DR. BULLIMORE: I'm looking at the IDE--for example, in the IDE protocol which is given in Table 6.4.1, which is on page 8 of the Medical Officer's Review, we have no eyes above 13 diopters and only 13 out of 640 above 11

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diopters, so somewhat arbitrarily, I would suggest 10 diopters as an alternate cut-off point.

DR. McCULLEY: How many eyes between minus 10 and 11, and between 11 and 12?

DR. BULLIMORE: Eighteen.

DR. McCULLEY: Eighteen between 10 and 11?

DR. BULLIMORE: Yes, out of a total of 640; that's for spherical correction only. It might be prudent to look at the spherical plus astigmatism tables, which I am trying to find.

DR. McCULLEY: Okay. Rather than spend more time with this, can we leave it just a little bit loose, that we are not comfortable above minus 12, and that comfort level, based on further analysis, might be somewhere between 10 and 12, and no more than 3 diopters of astigmatism? Is that adequate response for you?

DR. ROSENTHAL: Yes.

DR. McCULLEY: Thank you.

Are there any other dissenting views?

[No response.]

DR. McCULLEY: Okay.

Question Number 8. "Labelling for myopia equal to or greater than minus 7. If you feel that approval is indicated for myopia equal to or greater than minus 7, how

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should the labeling be approached?"

DR. MACSAI: We answered that.

DR. McCULLEY: Well, we put limits on it. Are there any other labeling issues that would go with those new limits?

Dr. Sugar?

DR. SUGAR: I think the labeling should specifically state outcomes stratified by degree of myopia in both the physicians and the patients booklets.

DR. McCULLEY: I think we have made similar suggestions before.

Dr. Macsai?

DR. MACSAI: And the percentages of retreatments required in those groups.

DR. McCULLEY: Presumably, if it's different from the lower, which I believe it was.

DR. MACSAI: Right--well, even if it is the same.

DR. McCULLEY: Even if it's the same--well, then, it would be covered in that other statement that we made relative to percentages with retreatment.

DR. MACSAI: Okay.

DR. McCULLEY: Concurrence? Okay.

Question Number 9. "Based upon the clinical investigation, has this PMA provided reasonable assurance of

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safety and effectiveness of this single device for the correction of low to high myopia with and without astigmatism? If not, does the Panel feel that a complete analysis of IRB Group 1 eyes (accountability of 95.3 percent at 6 months or later) by FDA would provide such assurance?"

The answer to the first part of this question really is what our final motion will be, so I don't think that now is the appropriate time to address that. There is the second part of the question--"Does the Panel feel that a complete analysis of IRB Group 1 eyes (accountability of 95.3 percent at 6 months or later) by FDA would provide such assurance?"

Dr. Bullimore?

DR. BULLIMORE: My preference would be that the accountability be elevated in the IDE group, particularly since there have been some albeit modest modifications in surgical techniques, and we base our decision on the IDE data rather than going back to a subset of the older data.

DR. McCULLEY: And remembering back, there has been a time that a suggestion for improving accountability was to pull out all stops and track the patients down. It was not shared with us what the results of that were; that was done in-house by FDA. But I think that improving accountability by whatever mechanism is necessary is one of

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the major messages that is coming through on the IDE population, I believe.

Dr. Pulido?

DR. PULIDO: I would even be happy with the entire IRB population, but one of the two populations should have better accountability, and it should not just be a subgroup of either one of those.

DR. McCULLEY: Is there concurrence with that last statement? That, then, answers the last question, and prior to asking for a motion, I would like to give sponsor another opportunity to respond to the last three questions that we have just addressed.

Dr. Kremer?

DR. KREMER: With regard to the question of the upper limit for myopic correction, perhaps we can look in more detail, but I believe the table that was referenced is specifically showing cases of spherical correction in those higher myopic ranges, and there is an additional table that shows the correction for those patients with higher spherical equivalent myopia that also had astigmatism. And that does increase the "n" for the number of patients in that very high range, and we would just request that perhaps consideration could be given to that when looking at that upper range.

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Also, although we feel that the results that we have stated are sufficient and valid to demonstrate safety and efficacy, if there is consideration given to looking at these other groups, that first group within the first cohort that was referenced, that follow-up was done way back when, when that was the only group that existed. Nobody went back later and said, okay, we're just going to follow up one group. So I don't believe there is any bias in that; it was simply done because those were the first U.S. LASIK patients, and the patients as well as ourselves were able to put more effort into getting more of those people back in and seeing the higher accountability.

Thank you.

DR. McCULLEY: Thank you.

I think in fairness, what I would like to do now is ask the Panel if there are any recommended changes in our previously proposed responses to the questions based on discussions, comments, that have taken place since we answered the individual questions.

Is there anyone who would like to propose a change in our previous response to any question?

Dr. Macsai?

DR. MACSAI: I have a concern regarding the retreatment and labeling question. Even if we look at the

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best reported group, that being Group 1 in the IRB protocol, "all eyes, one or more LASIK treatments," it appears that 5.8 percent of those eyes had a best spectacle corrected visual acuity worse than 20/25 if 20/20 or better preoperatively.

Now, if the study was conducted using a Snellen chart, my understanding is that if you are worse than 20/25, you have lost 2 lines if you started off at 20/20. So that 1.6 percent loss of greater than or equal to 2 lines best special corrected visual acuity would not be an accurate representation of the safety of this procedure.

DR. McCULLEY: I think that that would be a point that we would want the FDA to take into consideration in further review, analysis, labeling decisions.

DR. MACSAI: I don't know if that's labeling or safety. I'll let the FDA decide.

DR. McCULLEY: Okay, we'll let the FDA decide.

Other comments?

[No response.]

DR. McCULLEY: The next thing we are going to do is Ms. Thornton is going to read to us what our options for recommendations are, but before we go to that, I want to ask the FDA if there are other issues they would like the Panel to discuss or address.

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MS. BROGDON: Both Dr. Rosenthal and Dr. Waxler say there are no more issues.

DR. McCULLEY: Okay. Dr. Jurkus?

DR. JURKUS: I just have one concern regarding the proposed labeling, and that is the inclusion of keratoconus without thinning.

DR. McCULLEY: Good point.

DR. JURKUS: I would certainly be opposed to having that in the proposed labeling.

DR. McCULLEY: Good point. That was in our discussion, but it was not restated.

Okay. Sally, would you like to read to us our alternatives?

MS. THORNTON: I'd be glad to.

I know that Dr. Morris Waxler has gone over this previously, but I would like to state it again for the record. Your recommendation options for the vote are as follows: approval with no conditions attached, meaning that the agency, if they agree with the recommendation, will send an approvable letter to the applicant; approvable with conditions--you may recommend that the PMA be found approvable subject to specified conditions such as resolution of clearly-identified deficiencies which have been cited by you or by the FDA staff. Prior to voting, all

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of the conditions are discussed by the Panel and listed by the Panel Chair. You may specify what type of follow-up to the applicant's response to the conditions of your approvable recommendation you want. For example, FDA would handle it in-house, or Panel would handle it by homework assignment. Panel follow-up is usually done through homework assignment to the primary reviewers of the application or to other specified members of the Panel.

A formal discussion of the application at a future Panel meeting is not usually held.

If you recommend post-approval requirements to be imposed as a condition of approval, then your recommendation should address the following points: a) the purpose of the requirement; b) the number of subjects to be evaluated; and c) the reports that should be required to be submitted.

If the FDA agrees with the Panel recommendation, an approvable with conditions letter will be sent.

Not approvable--of the five reasons that the Act specifies for denial of approval, the following three reasons are applicable to this Panel's deliberations: the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended or suggested in the proposed labeling; reasonable assurance has not been given that the device is effective under the

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conditions of use prescribed, recommended or suggested in the labeling; based on a fair evaluation of all the material, facts, and your discussions, you believe the proposed labeling to be false or misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify the measures that you think are necessary for the application to be placed in an approvable form. If FDA agrees with the Panel's not approvable recommendations, we will send a not approvable letter.

This is not a final agency action on the PMA. The applicant has the opportunity to amend the PMA to supply the requested information. The amended application will be reviewed by the Panel at a future meeting unless the Panel requests otherwise.

Tabling--in rare circumstances, the Panel may decide to table an application. Tabling an application does not give specific guidance for the Panel to FDA or the applicant, thereby creating ambiguity and delay in the progress of the application. Therefore, we discourage tabling of an application.

The Panel should consider a not approval or approvable with conditions recommendation that gives clearly-described corrective steps. If the Panel does vote

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to table a PMA, the Panel will be asked to describe which information is missing and what prevents an alternative recommendation.

Following the voting, the Chair will ask each Panel member to present a brief statement for the record outlining the reasons for their vote.

Thank you, Mr. Chairman.

DR. McCULLEY: Thank you. I will now entertain a motion on this PMA.

Dr. Pulido?

DR. PULIDO: I'd like to make a motion for disapproval barring more accountability.

DR. McCULLEY: I think the wording is "not approvable."

DR. PULIDO: Not approvable.

DR. McCULLEY: Is there a second to that motion?

DR. MACSAI: Second.

DR. McCULLEY: Is there further discussion?

Dr. Bullimore?

DR. BULLIMORE: Well, I'm going to show my hand and say I am going to vote against this motion, and I'll speak against it.

I think, based on the number of patients that have been included and the potential to improve the

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accountability with a little bit more work, I consider this PMA to be approvable with conditions, and that's how I'm going to vote.

DR. McCULLEY: Okay. Are there other--please--other views, other comments or statements?

Dr. Macsai?

DR. MACSAI: My concern remains this accountability and therefore safety issue, and I can't stress enough that when we looked at these tables of results in the past, we were frequently looking at results reported in ETDRS charts, where 2 lines of visual loss is quite different than in the Snellen chart. Some sponsors represent this in letters lost, some in lines. But if we look at Snellen acuity, and we look at lines lost, and you have best spectacle corrected visual acuity worse than 20/25, and you start out at 20/20, that's 2 lines loss of vision.

Therefore, that bottom line, even on Group 1, which is "all eyes with the highest accountability," 5.8 percent of the patients really lost 2 lines of spectacle corrected visual acuity, which falls outside the guidance document.

DR. McCULLEY: Okay.

Dr. Higginbotham?

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DR. HIGGINBOTHAM: I acknowledge the sponsor's comments regarding the acquisition of data in a community-based fashion. However, I think there are some things that one can do to try to standardize the acquisition of data, and one of those things is just to have an agreed-upon set of definitions.

Having several hundred practitioners follow the patients, I think really contaminates the purity of the data, and if there are limited numbers of practitioners who actually are certifiable by some set of standards, then I think I would feel more comfortable about the data, but I have concerns about the purity of the data at this point.

DR. McCULLEY: Other comments, one direction or the other, from anyone?

[No response.]

DR. McCULLEY: Motion to call the question?

DR. MACSAI: I call for the question.

DR. McCULLEY: The motion is to recommend not approvable. All in favor of that motion signify by raising your right hand.

[A show of hands.]

DR. McCULLEY: That is 4.

All opposed to the motion signify by raising your right hand.

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[A show of hands.]

DR. McCULLEY: Two.

So a vote of 4 to 2 in support of the motion to recommend not approvable. The motion carries.

Now, our order here would be to state--okay, "If you recommend that the application is not approvable for any of these stated reasons, then we ask that you identify the measures that you think are necessary for the applicant to be placed in an approvable form."

Dr. Macsai?

DR. MACSAI: I make this comment in reference to that made earlier by Dr. Marcia Yaross. I think she made an excellent point, that we need to be fair and equitable in our accountability, and that if we have set 90 percent as the standard, it should apply to all applications. If the accountability falls below it, it is very difficult as a person who is reviewing it to determine the safety and efficacy.

Therefore, I would ask that the sponsor improve their accountability to the 90 percent level to determine safety and efficacy.

DR. McCULLEY: Our order should have been for us to state the reasons that we voted in the manner in which we did prior to addressing this issue. We will leave on the

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record Dr. Macsai's response so she doesn't have to say it again, but let's start with Dr. Bullimore and go around, and please state succinctly why you voted as you voted.

DR. BULLIMORE: I am in total agreement with comments made by Drs. Macsai and Higginbotham in the last few minutes. I am very nervous about approving or judging a PMA to be approvable with or without conditions when the accountability is so low. My concern is that next time we come back and convene, we'll be presented with lower and lower levels of accountability until we have been completely undermined, and I think we have got to make some attempt to maintain standards.

I do respect the energies that the sponsor has put forth in terms of trying to identify the sources of bias, but you can't identify sources of bias from patients who are missing, and when that number is greater than 10 percent, the comfort level of myself and my colleagues on the panel is presumably undermined.

I would consider good accountability to be based on patients examined at or after 6 months, so I don't think it's necessary to deep-six this proposal based on the fact that only 60-something percent were examined within the 6-month window. However, if we are going to broaden the window to 6 months or later, I think we need to at least

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hold it to the 90 percent standard recommended by this Panel.

I share Dr. Higginbotham's concern about a--I think she used the word "community-based"--PMA. I think strategies that are effective at building a strong and successful practice and referral network and co-management may be conducive to the above, but they are certainly not conducive to the collection of good-quality scientific and clinical data, and I would urge the FDA to make that clear to other prospective sponsors.

I think this PMA should be reconsidered at a later date, and I encourage the sponsors to make it better and really thank them for their efforts.

DR. McCULLEY: Thank you.

Dr. Sugar?

DR. SUGAR: I voted for the motion against approval on the basis that the data acquisition was inadequate, the accountability was inadequate, there was--again, looking at the guidelines--lack of, as the guidelines recommend, cycloplegic evaluation at 6 months, concern about induced cylinder, and lack of adequate information thus far on stability. These are safety and efficacy issues.

DR. McCULLEY: Thank you.

Dr. Macsai?

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DR. MACSAI: I concur with Dr. Sugar's comments. In addition, I voted against approval based on significant concern about these hyperopic retreatments, potential overcorrections and lack of cycloplegic refractions as outlined at 6 months in the guidance document, and a safety concern of loss of vision in patients.

DR. McCULLEY: Thank you.

Dr. Pulido?

DR. PULIDO: Mr. Chairperson, I tried to follow Sara Thornton's guidelines and had mentioned when I made my recommendation my reason why, but for the record, I will repeat it. It is because of my concerns also about the accountability, and we now have a separate problem in that even if they can retrieve back the patients who were not accounted for at 6 months, we will not be able to have good stability data because it would have been way out past 6 months once they are back.

DR. McCULLEY: Dr. Higginbotham?

DR. HIGGINBOTHAM: I voted for disapproval. The devil is in the details, and the data acquisition issue I think needs to be addressed as well as accountability.

DR. McCULLEY: Thank you.

Dr. Jurkus?

DR. JURKUS: I voted against nonapproval because I

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did not see from the data that this was totally unsafe or totally ineffective; and in terms of the data that was presented, I think more accountability would add to the information, and I would like to see it revisited.

DR. McCULLEY: Thank you.

That completes the polling. Now my question here is to what detail should we go. We have addressed nine and added other issues in our questions from the FDA. I would hope that with Dr. Macsai's statement and a reference to our responses to the questions posed by the FDA that that would address the need that is stated in the regulations.

Is that acceptable to the FDA?

MS. BROGDON: I have some qualms about this, Mr. Chairman. I think we have understood your discussion and your answers to the questions. I think that since the motion that passed is for disapproval, we don't have to hold out for another enumeration of what the deficiencies are, so I think we are okay.

DR. WAXLER: I would only add that perhaps you might be explicit in saying that your answers to the questions constitute the list of deficiencies or conditions that you wish us to communicate to the sponsor.

DR. McCULLEY: I think we can make that explicit. You stated it well. We won't restate it.

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Dr. Sugar?

DR. SUGAR: I'd like to add a request for post-treatment cycloplegic data, which is still acquirable, I presume.

DR. McCULLEY: Other comments?

Dr. Higginbotham?

DR. HIGGINBOTHAM: I know this comment has been made, but not in the context of the questions. I would suggest some certification protocol for practitioners, and perhaps limiting the number of practitioners to something less than several hundred, just so you can improve the quality of the data acquisition.

DR. McCULLEY: Other comments?

Dr. Rosenthal, do you have any comments?
Otherwise, we are going to adjourn.

DR. ROSENTHAL: Yes. I would tactfully like to ask the Panel a question. I'm still new to the game, but I understand that because this has been voted as a disapprovable--

DR. McCULLEY: Not approvable.

DR. ROSENTHAL: --not approvable--that it has to come back to Panel, and I am wondering if that is an absolute must or, because we have now considered this issue on more than one occasion, would it be sufficient and would

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it be allowable if the FDA would be allowed to deal with these issues and not keep coming back, over and over?

DR. McCULLEY: You asked a question along those lines once before, tactfully, and I think the tactful response--I believe it was the same question--was that that is very difficult to answer in the absence of data. I don't know.

Dr. Bullimore?

DR. BULLIMORE: I believe Ms. Thornton should answer this question. Is it mandated that we--

MS. THORNTON: I believe that--the way it is sated in the materials that I have, it seems to be that it is much more of a mandate than a choice. However, we would need to go back to the regulations to establish whether or not there is a specific thing that says this must happen.

I'd like to ask Ms. Nancy Pluhoski [ph], if she is available--I know she has been here and has possibly stepped out--but that is something that has not come up before.

DR. McCULLEY: Just my understanding of this, from a comfort level, I think, in this new area, we have not gotten to the point where we say this is what we would like to see. Until we do that, I am a little uncomfortable saying that I would not want things to come back to Panel. But on the other hand, the agency decides what you bring to

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us for scientific advice and what you don't.

DR. ROSENTHAL: And we have brought two PMAs relating to this issue to your attention; we have received sufficient information from both of them--this may be a moot point, because we've just had a ruling.

DR. McCULLEY: It may be.

MS. THORNTON: Excuse me. We have just had another referee come in. It is up to you. It is at your discretion. It is not in the regulations.

DR. McCULLEY: Up to whom? The FDA?

MS. THORNTON: No; to the Panel.

DR. McCULLEY: As to whether we want to see it again, that we come back?

MS. THORNTON: No--sorry--it's up to FDA. I'm sorry.

DR. McCULLEY: To decide whether they bring it to us. That's what I thought. I mean, we serve at your pleasure, and we do what you ask us to do.

MS. BROGDON: But if you have a recommendation one way of the other, we'd like to hear it.

DR. McCULLEY: Okay, I'll jump on that one, but Dr. Bullimore, you were first, I think.

DR. BULLIMORE: I'll defer to Dr. Sugar.

DR. McCULLEY: Dr. Sugar?

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DR. SUGAR: I think that this could go as a homework assignment to a portion of the Panel rather than the full Panel--assuming it's okay with FDA.

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: I think I am thinking along the same lines as Dr. Rosenthal here. We've seen two of these with very similar issues, and I think we have clearly identified what the limitations of the data are that we've been presented with today, and I am confident that if the FDA can make a decision as to whether they can bring something to Panel, they can make a decision the other way.

DR. McCULLEY: Yes. My impression is that you'd bring it to us if you want, so I guess my question to you is do you think we have given enough input to you that you wouldn't need us to review another application, or are we still bringing up different issues that you had not anticipated and that you would feel that it would be of value to bring it back to us? It's your decision.

DR. ROSENTHAL: I asked that question because I have such respect for the Panel that I did not want to not do something that would be in their demand; and so if you will leave it up to the agency to make the decision, that would be a perfectly satisfactory agreement.

DR. PULIDO: I so move.

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DR. McCULLEY: I think there is agreement there.

DR. ROSENTHAL: Thank you very much.

DR. McCULLEY: Okay. Can we now break for lunch?
Okay. I have 1:05. Let's reconvene at 1:45, and afternoon
sponsor, please take note.

MS. THORNTON: Would the Panel please take the
documents to the back of the room that they are not going to
need for the afternoon session--anything from the morning
session that is considered confidential information has to
be shredded. Please take them to the bins at the back of
the room.

[Whereupon, at 1:05 p.m., the proceedings were
recessed, to reconvene at 1:45 p.m. this same day.]

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AFTERNOON SESSION

[1:45 p.m.]

DR. HIGGINBOTHAM: Good afternoon. We're going to start the afternoon session. I hope everyone had a wonderful lunch, and we'll get home shortly, hopefully.

We'll start the session this afternoon with Dr. Morris Waxler. Dr. Waxler, would you introduce the next PMA?

DR. WAXLER: Thank you, Dr. Higginbotham.

This is Autonomous Technologies' PMA P970043.

The fact that this laser is a scanning laser with an eye-tracker is important to FDA from the standpoint of an engineering perspective. However, the Panel is not being asked to evaluate this technology but rather to provide expert advice to FDA on whether the clinical outcomes presented in this application demonstrate a reasonable assurance of safety and effectiveness of this device.

This application stands on its own. Please do not compare it to other lasers for refractive surgery, either those that have received PMA approval or that are under review. I urge each Panel member to use your own clinical knowledge and experience to arrive at your own recommendation as to whether there is a reasonable assurance of safety and effectiveness of this device.

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In areas such as astigmatism where there is no FDA guidance, you are urged to discuss fully the practical implications of any analyses, such as vector analysis, that have been conducted or that you may recommend be conducted--what are the implications for the patient? Can potential problems be addressed by cautionary labeling, or should the applicant modify the device to prevent such problems from occurring?

Ms. Daryl Kaufman is the Team Leader for P970043. She will present a brief history of this application and introduce the speakers.

Daryl?

MS. KAUFMAN: Good afternoon. I am Daryl Kaufman, the Team Leader for PMA 970043, submitted by Autonomous Technologies, Incorporated.

The device which is the subject of this PMA is a scanning excimer laser for refractive surgery which uses a .40 to .45 millimeter gauseum [ph] beam to shape the cornea as it scans the surface and uses an eye-tracking system to enable the laser scan to follow circadian movements of the eye.

The sponsor is requesting the T-PRK laser system indication for the correction of minus 1 to minus 10 diopters of spherical myopia with or without 6 diopters of

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astigmatism at the spectacle plane, the combination of which must result in attempted correction between minus .5 diopter and minus 10 diopter spherical equivalent at the spectacle plane where sphere or cylinder is at least 1 diopter.

Six hundred seventy-eight subjects were enrolled as the primary cohort prior to May 30th, 1997 at six sites. A continuing cohort of 93 subjects was enrolled between June 1st, 1997 and October 10th, 1997.

The clinical study for PRK with this laser was submitted in IDE Application G950213 and was approved by FDA on January 3, 1996. The study was approved for expansion to seven sites and 500 subjects on September 13, 1996. On October 15, 1996, ATC requested a continuation of the study with another argon fluoride laser head called the beta unit as a replacement for the original alpha unit laser head. This was approved by FDA on November 12, 1996.

A sub-study was conducted by the sponsor where subjects treated with the alpha or beta units were analyzed separately, and a comparison table and outcomes was included in the clinical data you have reviewed.

The astigmatism protocol was approved by FDA on December 11, 1996. The PMA Application P970043 was submitted to FDA on September 5, 1997, and a filing letter acknowledging that the application was sufficiently complete

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to permit a review was sent to the sponsor on October 17, 1997.

The primary Panel reviewers for this PMA application were James P. McCulley, M.D. and Mark A. Bullimore, MCOptom, Ph.D. Panel input is required because clinical judgment is necessary to evaluate this data to help assess the safety and efficacy of the device for the intended indications and the stated refractive ranges.

The reviewing team evaluating this PMA application and related amendments include the following reviewers. The statistical review was completed by Dr. Judy Chen. Patient information labeling was reviewed by Ms. Carol Clayton. Sharon Kalacarinias [ph] was responsible for handling the GNP [ph] assessments, and bioresearch monitoring input and inspections were handled by Jean Toth-Allen. Software/hardware evaluations were completed by John Murray, and the engineering reviews and evaluations were completed by Dr. Bruce Drum. And, last but not least, the clinical data was reviewed by Dr. Malvina Eydelman.

I thank all the reviewers including the primary reviewers for their expeditious and insightful evaluations. The sponsor will make their presentation of the PMA at this time, followed by Dr. Eydelman's discussion of her review.

DR. HIGGINBOTHAM: Thank you.

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If the sponsor would now approach the table, you have one hour. I have approximately 1:58; you have until 2:58 for your presentation. Please identify yourself.

MS. MCGARVEY: I am Shirley McGarvey. I am the paid regulatory consultant to Autonomous Technologies.

Could we have the lights out?

[Slide.]

I'd like to thank you for giving us the opportunity to provide you with some information related to our LADARVision Tracker-Assisted Narrow Beam Shaping Excimer Laser System.

After this introduction, the technology overview will be provided by Mr. Randy Frey, who is the CEO and founder of the company. I will then come back to the podium and talk a little bit about our study design and the changes in the FDA guidance document over time and how that impacted our study design.

The clinical results will be provided by Dr. Marguerite McDonald, who is the Medical Director for the company, and the response to primary reviewers' inquiries will be provided by Dr. Charline Gauthier. We have received these in the prior week, and we have information that we have provided back to the agency, and she will handle those questions to try to be expeditious.

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Mr. Randy Frey.

[Slide.]

MR. FREY: Thank you.

I'd like to discuss the LADARVision technology that is present in the system. The system is formally known as the T-PRK, tracker-assisted PRK. LADARVision is the title invoking the core laser radar technology of the company.

I'll briefly describe the technology development history that was associated--very brief on that--and then describe the two major technology elements that we are incorporating in the system--the high-performance eye-tracker and the narrow beam shaping technology.

[Slide.]

I am an electrical engineer. I spent 7 years in the military aerospace industry doing laser radar technology and laser radar tracking technology. I founded Autonomous in 1985, and a small group of about 8 to 10 electrical, mechanical and software engineers did laser radar technology development programs for the Government, mostly in research and development contracts with the Strategic Defense Initiative Organization, informally known as Star Wars, and also NASA. We developed tracking technology that included 6-degree-of-freedom tracking for adaptive grasping. We also

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addressed the issue of projecting a defined fluence on an object that may not want to be illuminated with that fluence with directed energy weapon technology.

The core technology that comes out of this is pointing and tracking technology.

[Slide.]

When we sought our initial design, we looked at what we saw as two major limitations in wide beam technology. One was that position errors from any source were not compensated. Therefore, we developed technology to track the eye during surgery. We also saw that there were issues with laser beam uniformity, and we sought a different approach to narrow beam shaping, with some new shaping algorithms that are patent pending. We also retained the 192-nanometer wavelength that has a long exposure in the research community.

[Slide.]

Regarding the tracking, it is important to note that the tracker does not automatically determine the center of the ablation. It is up to the physician to choose the center. We do recommend a pupil-centered approach and provide means for that in the system.

What we try to do, though, is reduce the variance about the physician-chosen center. Those sources of

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movement are typically head movement, fixation wander, respiration and heartbeat. And the element that really drives the performance of this system is the saccadic eye movement during fixation; these saccadic movements are very fast and require the band width of the tracker to be quite high.

We attempted to design a very robust/failsafe design that can stand the dynamics of the procedure, the changing corneal shape and corneal clarity that often occurs during surgery, and then the ablated debris that is coming up from the cornea. So we designed a very high-margin, high signal-to-noise laser radar sensor that was insensitive to spurious signals.

So this has the effect of minimizing the issue with interrupted procedures, and we also put in means to the system to pick up where we left off in the event, for any circumstance, the procedure were interrupted.

[Slide.]

This is a display of eye movement that we record with our tracking system during 10 seconds of fixation. What you see here are about 50 movements recorded in that 10 seconds, or about 5 saccades per second. The scale is blown up very large so you can see what happens when the tracker is not just in measurement mode, but enabled.

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[Slide.]

When the tracker is enabled, those very large-amplitude errors get reduced to this small basket. The two scales on the slides are the same, and the actual amplitude of saccadic movement is actually quite small, typically on the order of what is shown here.

[Slide.]

This is an example of the graphical user interface that the physician deals with when he uses the system. The image on the top left is a camera looking directly at the eye--it is the untracked view--and this image on the right looks through the tracker and is the tracked view.

When the "Track" button is pressed, the system does a scan and measures the pupil diameter automatically and measures all the parameters for that patient and optimizes the tracker accordingly; and then, for any movement that occurs here, as you see in this view, the tracker mirror moves to compensate. So the excimer scanning device does its shaping looking into this optically frozen view.

[Slide.]

The narrow beam shaping is a new concept from our perspective. We have implemented what one could think of as a pointillistic approach. You could envision a

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high-resolution photograph in a magazine, and the image quality of that is simply made up of the variation in dots on the page. Actually, if you look under a microscope, the shape of those dots does not really matter to the image quality; it is the relative positioning of those dots that matters. So the shape of the dots in our case relates to the shape of the laser beam, so this fundamentally reduces the dependence on laser beam uniformity and puts the dependence on the pointing accuracy of the system to position each shot in XY space very accurately with respect to one another. This is part of our core technology.

We also see that the flexibility that you get in the narrow beam shaping approach could perhaps offer the growth to customized ablations in the future.

[Slide.]

From a clinical interface perspective, the physician centers on the undilated pupil, and we provide a means, a computer-generated limbus ring, to store the center of the undilated pupil with respect to the limbus prior to surgery. We then have a geometry calibration that occurs, essentially, a pointing accuracy calibration that occurs at the eye plane--it is not up in the laser head.

In addition, the modality requires us to examine not the depth per shot but the volume per shot removal, and

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we have a calibration technique that calibrates the volume per shot for the system.

[Slide.]

Because the laser device itself is smaller than has typically been used in the past--the device itself is on the order of a shoebox size--the whole system is much more compact and more doctor-office-friendly, we believe.

[Slide.]

The narrow beam shaping from a laser tissue interaction has been worked very hard by the company. We did retain the 193 nanometer wavelength, and we also retained essentially the same average fluence for the procedure--around 200 millijewels per centimeter squared. What we find, though, with the lower energy is that you have a low acoustic force, and you can hear this difference in the surgery. We also find that the nature of the shot pattern which defines the endpoint on the shape is different from the extraction sequence--essentially, space versus time thought process. So what we do is we design the shot pattern to get to the right shape, but design the extraction sequence to optimize the tissue interaction in terms of these two parameters; so what we drive the pointing system to do is take very large steps between pulses and therefore avoid the plume on the previous pulse, and in addition take

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between 15 and 20 pulses before we revisit the same region of tissue again, giving a very long time for thermal relaxation to take place in the tissue. This avoids any additional thermal load that could be point on the cornea.

But with that, we have been able to achieve ablation times that are actually quite fast, less than 10 seconds per diopter. This is in between the two previously approved wide area systems. This has been done by very highspeed, accurate pointing technology.

[Slide.]

This is an example of the laser scanning and narrow beam shaping technology, not during a myopic correction, because straight spherical is a little bit boring visually--this is a hyperopic sphere with hyperopic cylinder simultaneously. So you see what emerges--this dual crescent shape is just an example of the shaping technology that we have employed.

Thank you for your time, and I'll now turn it over to Shirley McGarvey.

MS. MCGARVEY: I will review the chronology of our clinical studies and then assess the impact of the FDA Guidance Document as it changed over time on our study design. That provided us with the rationale for filing the PMA with 6 months' follow-up data on our primary cohort. We

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have additional follow-up data that you have seen in the file with good accountability at each of the subsequent intervals, and we will provide you with the information related to the stability question.

[Slide.]

Starting in 1994, the company had developed their products to the point where we are able to initiate preclinical and laboratory work, and we did primate studies. The results of this led us to initiate Phase I and Phase II-A studies in Greece.

From the minor modifications to the algorithm in the Phase II-A, we were able to launch into Phase II-B, and with the data from this study, we requested that we could open a clinical trial to confirm that Phase II data at a single site in the United States, and this was Dr. Marguerite McDonald's site.

Subsequent to this, with the data that was entered at that site, we opened the Phase III study with additional sites, and then we expanded the indication to minus 10 diopters sphere and minus 6 diopters with astigmatism.

The entry of the patients into the Phase III study started in October and ended at the end of May of 1997.

Subsequent to that, we have not entered additional patients into this study, but we have treated the fellow

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eyes of the remaining patients.

[Slide.]

Prior to 1995, there were several versions of the Guidance Document, and the Guidance Document called out several phases of clinical trials with long periods of follow-up requirement between each one of these. There were 24-month terms for Phase III; there were no defined performance criteria during that time, because not a lot was known; and they required an arbitrary number of greater than 500 patients in Phase III; they also required that some experimental procedures versus established clinical procedures be pursued, and even today, there remains some debate with respect to whether the contrast sensitivity and topography data can be reasonably analyzed in the aggregate to provide us better insight with respect to outcome.

[Slide.]

During the balance of 1995 after the July Panel meeting and through 1996, the FDA interacted with members of the professional societies as well as member of industry under the aegis of the Eye Care Technology Forum, and this resulted in the 1996 Guidance Document.

Explicit study phases were defined as not being necessary, sample sizes were statistically based, the key safety parameter was loss of best corrected VA, and

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effectiveness parameters were also established. And, most importantly from our point of view is that stability was defined and established as an objective criteria for study term.

[Slide.]

For PRK, the Guidance Document still calls out 12 months, and this was based on review of prior wide area excimer laser data. For LASIK, it was felt that 6-month follow-up was acceptable because the information was based from the literature that earlier stability meeting the definition could be attained.

You can see the definition at the lower part of the slide, and you can see that in our studies, the domestic spherical study, the astigmatism study and the foreign spherical study, between 3 to 6 months, 96.5 percent of the domestic spherical patients meet these criteria; of the domestic astigmats, 97.3 percent met the criteria, and for the foreign spherical study, 99 percent of patients met the criteria.

[Slide.]

So the rationale for filing the PMA with 6-month follow-up on our primary cohort is based on stability of the refractive outcome between 3 and 6 months. We have additional support from the foreign study and 12-month

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follow-up and complete subgroup analyses on contract sensitivity and endothelial cell microscopy. We have excellent accountability at all key intervals, and the clinical results that will be reported to you by Dr. McDonald exceed all the FDA performance criteria and exceed those that were reported as the basis for approval for prior approved excimer laser systems.

[Slide.]

This is the objective criteria that the 1996 Guidance Document calls out, and these are the parameters against which we will be measuring our performance, and Dr. McDonald will provide this.

The performance relative to prior approved excimer lasers is data required from published safety and effectiveness summaries and from Panel videotapes.

Dr. McDonald?

DR. McDONALD: Thank you, Shirley.

I am Dr. Marguerite McDonald. I am the Medical Director of Autonomous Technologies. I am a paid consultant for the company, and my travel here today was paid for by the sponsor as well.

[Slide.]

We are asking for approval for and labeling for PRK treatments for the reduction or elimination of mild to

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moderate myopia for minus 1 to minus 10 diopters of sphere, up to 6 diopters of astigmatism, with a spherical equivalent between minus .50 and minus 10, at the spectacle plane where sphere or cylinder is at least 1 diopter in subjects with documented stability of refraction for the prior 12 months defined as less than or equal to .50 diopter of change for up to 7 diopters and less than or equal to 1 diopter of change for more than 7 diopters in subjects who are 18 years of age or older.

[Slide.]

If you look at our enrollment by site in the United States, we had six sites. We had 11 principal investigators in total, and you can see that for our enrollment for the spheres and the astigmats, we had a nice distribution percentage-wise among all six sites.

[Slide.]

Here are our treatment parameters. For our spheres, we treated from minus 1 to minus 10 sphere only; cylinder, up to minus .75; spherical equivalent never exceeded minus 10, and our optic zone was 6 millimeters.

For the astigmats, we treated between minus 1 and minus 9.75, with cylinder between minus .50 and minus 6; the spherical equivalent never exceeded minus 10, and their optical zone was 5.5 by 7.5 millimeters.

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All treatments were based on manifest refraction, and for our astigmats, our cylinder axis was screened carefully for consistency.

[Slide.]

Postoperatively, our original protocol called for Protek as the bandage contact lens; Voltaren and Tobradex as the NSAID, steroid and antibiotic combination, which were used until the eye was healed; and during surgery, a rotating brush was used for epithelial removal. We gave no additional steroids until the one-month postop gate, when a decision tree was used, and based on their refraction, they either got steroids or did not.

[Slide.]

Here, you see the refractive parameters on the left. Spherical equivalent in intervals of 1 to 2 diopters, 2 to 3, et cetera, all the way up to 10 diopters.

Here is the recruitment of spheres into the study and astigmats, and here on the far right, you see the U.S. Census as published by Roberts in 1978 of all U.S. myopes at that time. And you can see that we actually recruited a much higher percentage of high myopes into our cohort than existed percentage-wise in the U.S. population of myopes.

[Slide.]

Here is our domestic primary cohort at months as

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far as accountability. We had 467 spherical eyes and 211 astigmats enrolled. Eight eyes were discontinued in each group--and I'll discuss them in detail; 19 spheres missed their visit at 6 months, and one astigmat. We had 23 spherical eyes in process, and 15 astigmatic eyes. What that means is the patients were still in their interval to be seen; they had not missed the visit, but we closed the database to get ready for this Panel meeting.

I must say that since that time, in the supplementary information that you were given on January 23, all but one spherer has now been seen, and all but 3 astigmats. So this "in process" number is much smaller for the supplemental information you have.

All in all, we have 95.6 percent accountability for our spherers and 99.5 percent for our astigmats.

[Slide.]

Our sample size at 6 months. The "n" is always 417 for the spherers and 187 for the astigmats, except when we are talking about uncorrected vision; then, we take out 28 spherical monovision patients and 10 astigmats who wanted monovision, and our "n" for that only is 389 for the spherers and 177 for the astigmats. These numbers more than meet the calculated sample size required.

[Slide.]

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If we look at our sample size in comparison to the sample size to the sample size for the approved excimer lasers, here you see our 6-month cohorts for the spherers and the astigmats in white in the first column, versus the sample size for Approved Laser A at 6 months and Approved Laser B in 6 months here in yellow in the far right column. You can see that we are equal in size, if not larger.

[Slide.]

Now, discontinued eyes. These were eyes that were followed, but the data was not included in the primary cohort after their exit. The reasons fell into two groups--not laser-related or laser-related. Not laser-related included 5 people who were diagnosed as pregnant after they had been enrolled in the study, one person who was diagnosed with insulin-dependent diabetes after being enrolled, and one death.

Laser-related discontinuances included 9 retreatments in the spherers and 8 in the astigmats, whom we will talk about in detail in a moment, and one person in the spherical cohort who had a secondary procedure after an adverse reaction, and we will also discuss that in some detail.

[Slide.]

Demographically, for our spherers and our

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astigmats, we had more females than males in both groups, and although most of our patients were Caucasian, all the races were well-represented.

[Slide.]

Our patients were a little older on average than previous cohorts presented to you for Approved Lasers A and B. On average, our spherers were 5 to 6 years older, as well as our astigmats, than previous cohorts. They were 40.6 years and 42 years on average, respectively, for the spherers and the astigmats. If we look down here on a history of contact lens wear, we find that 77 to 88 percent of our patients wore contacts before they entered our study.

[Slide.]

Effectiveness at 6 months. Here, you see uncorrected visual acuity, 20/20 or better, 20/25 or better, 20/40 or better uncorrected, and our spherical data and our astigmatic data on the first two columns. The blue column on the far right is the FDA guidance criteria which has been set only for under 7 diopters, and we treated up to 10 of sphere and 6 of cylinder. Nonetheless you can see that we nicely meet these criteria which were set for a much lower range of myopia.

Here, we have 69.7 percent 20/20 or better uncorrected in our spherers; and 59.3 percent in our

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astigmats.

[Slide.]

Here is a data format that I am going to use several times in the course of my presentation. Here is the percentage of ATC patients treated for 1 to 10 diopters of spherical myopia in white in the first column, compared to the 1 to 7 diopter myopes treated for Approved Laser A, versus the 1 to 6 diopter myopes in yellow treated for Approved Laser B, versus the 1 to 7 diopter myopes treated with the approval LASIK cohort that was presented to you 6 months ago. We only have 12-month data for that group. Everything else is 6-month data, but that is not in the public domain, so we had to turn to 12-month data.

And then, for astigmatism, here is the ATC astigmatism cohort, treating up to 10 diopters of sphere and 6 of cylinder, versus Approved Laser B, which was approved for treatment up to 6 diopters of sphere and 4 diopters of cylinder. And here you can see that across the board, the ATC cohorts had the highest percentage, 20/40 or better at 6 months, and there in orange is the FDA guidance criteria for less than 7 diopters,

[Slide.]

Now, it is well-entrenched in ophthalmic folklore that you cannot treat above 6 diopters of myopia without

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turning to LASIK, and here, we are doing an apples-to-apples comparison. We took only our 7 to 10 diopter myopes--here they are--our spherers from 7 to 10 in white, our astigmats in blue--and we looked at the 7 to 10 diopter myopes--this is 3-month data only because we didn't have 6-month, so we're looking at 3 months for the 7 to 10 diopter myopes treated with the approvable LASIK cohort. And you can see that perhaps we'll have to change our mind about that as the surface technology, modern technology, appears to give a good result even in moderate myopia, and that seems to exceed the results with LASIK.

[Slide.]

If we look at uncorrected 20/20 or better at 6 months, the same across-the-board comparison, you see we have 69.7 percent of our spheres, 59.3 percent of our astigmats, versus all the other LASIK and approved PRK cohorts, and you can see that the ATC data surpass the others.

[Slide.]

If we look at how many people ended up with better uncorrected vision than they had preop best corrected-- George Waring has said that refractive surgery will truly come of age when we can provide that level of correction to people--here, you see 19 percent of our spherers attained

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that goal and 23 percent of our astigmats. This was not just a magnification effect. Of course, we didn't include monovision eyes in this. But in this spherical group, only 5 percent of these people were above 7 diopters myopic, and only 20 percent of our astigmats. So this is truly a laser-related effect.

[Slide.]

Let's look at uncorrected vision stratified by preop diopters of astigmatism. Here is our uncorrected vision, and here is preop cylinder 0 to 1, 1 to 2, 2 to 3 and 3 to 6. We can see our percentages across the board show a very consistent performance for this laser, right up to the highest cylindrical corrections.

[Slide.]

If we look at our uncorrected acuity, once again stratified by preop diopters of astigmatism, 0 to 1, 1 to 2, 2 to 3, and 3 to 6 here is the Autonomous data, the percentage uncorrected 20/20 or better in white, versus Approved Laser B over the same range. And you can that while Approved Laser B becomes less effective, there is a consistent performance for the ATC cohort.

[Slide.]

Let's look at manifest refraction. here is plus or minus .50 and plus or minus 1 for our spherers and our

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astigmats at 6 months. Here, once again, is the FDA Guidance Document for less than 7 diopters--and we treated, as I said before, up to 10 of sphere and up to 6 of cylinder--and you can see that we nicely meet the FDA specifications, though they were set for a lower degree of myopia.

[Slide.]

Once again, we are going to compare the percentage of our patients who are plus or minus .50 at 6 months versus Approved Lasers A and B, approvable LASIK cohort, and here is the FDA guidance benchmark again in orange, and you can see that the ATC percentages are the highest.

[Slide.]

And if we look at plus or minus one diopter, even with that widened gate, you can see that the ATC performs at the highest level.

[Slide.]

Let's look at moderate myopes again, 7 to 10 diopter myopes, for dioptric accuracy. The FDA guidelines once again for below 7 are that 50 percent of the patients have to be plus or minus .50, in yellow, and 75 percent of the patients have to be plus or minus 1, in orange.

Here, you see our spherical results on the left and our astigmats on the right, and we more than meet these

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criteria that were set for lower myopia.

[Slide.]

Let's look at dioptric accuracy stratified by diopters of preexisting astigmatism. Here is plus or minus .50 and plus or minus 1, and preop cylinder from 0 to 1, 1 to 2, 2 to 3, and 3 to 6. Once again, we see a very consistent performance across the entire range of preoperative cylinder.

[Slide.]

Let's also look at the FDA definition of stability. This was defined in the 1996 Guidance Document as "A change of less than or equal to 1 diopter of manifest spherical equivalent refraction between two refractions performed at least 3 months apart."

So here are our spherers and our astigmats and the FDA Guidance Document, and you see that we meet that criteria; and down below, our 95 percent confidence intervals are very tight and much less than 1.

[Slide.]

Now our scatterplots of attempted versus achieved, and this is, of course, the ideal result in the middle, the solid line, and the hatched fuschia lines represent plus or minus 1 diopter. Here, you see our spherers in yellow and our astigmats in white, and you can see a little

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overcorrection at one month; at 3 months, that has started to decrease, and at 6 months, the scatter is pretty tight--a little wider up here, but pretty tight--and only one or two seriously undercorrected people.

[Slide.]

Let's look at the manifest refraction over time. Here is postoperative months, here is the refraction. You can see that the patients become hyperopic, but only slightly and for a short period of time. This differs tremendously from earlier technology. In the early days, you would become half as hyperopic in the first few months as you had been myopic, and you would stay up there for a long time. This is especially important because the patients tend to be older--40-, 42-year-olds appreciate not being hyperopic for a long time.

So here is the 6-month population, and now we'll pop in in yellow the 9-month population, and in white the one year-population, and in red, the 18-month population. And this demonstrates nicely the stability that starts at 3 months and is maintained over time.

[Slide.]

Let's look at the summary of cylinder correction at 6 months. Here you have the scalar or absolute values; here is vector analysis in the middle, and on the far right,

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the ideal numbers we would like to see.

By scalar analysis, preoperatively, they had 1.42 diopters of astigmatism; we achieved a 1.15 diopter correction on average; postoperatively, they were left with a third of a diopter, and this was a 79 percent achieved correction. This compares nicely with Approved Laser B, which had 67 percent achieved correction at 6 months.

Our average axis shift for those who had any astigmatism after surgery was 31.7 degrees.

By vector analysis, we intended to correct 1.42 diopters; we achieved a correction of 1.36. The difference is still about a third of a diopter. But by vector analysis, we have 96 percent achieved correction, with an angle of error of only 4.9 degrees.

The index of success is calculated as C divided by A, and the closer to zero it is, the better--that's the ideal. Ours was fairly close to zero, at 0.24.

So this indicates basically that the laser was performing as it should, but there was a little problem with axis, which was either caused by inaccurate measurement preoperatively or a slight alignment error during surgery.

[Slide.]

Let's look at vector analysis stratified by diopter. Here is preop cylinder from .5 to 1, 1 to 2, 2 to

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3, and 3 to 6. The percent achieved maintains the same level all the way across that entire range, percent achieved correction. Our angle of error is very low and stays low, and our index of success comes very close to zero.

[Slide.]

Cylinder magnitude at 6 months. We can tell our patients that they have 81.3 percent likelihood of being .50 or less diopter astigmatic--in other words, 81.3 percent of our patients ended up with .50 diopter or less at 6 months. That was 94.7 percent 1 diopter or less at 6 months.

[Slide.]

Let's look at one big summary table of the effectiveness at 6 months. Here is all the spherical information, the astigmatic information, versus the FDA Guidance Document for under 7 diopters. We can see that although we attempted to correct a much wider range of refractive error, our uncorrected vision, manifest refraction plus or minus .50 and plus or minus 1, and our stability, more than meet these criteria.

[Slide.]

Safety data at 6 months. Here you see the loss of 2 or more lines of best corrected vision for Autonomous spherers, Approved Laser A, Approved Laser B, approvable LASIK cohort, our ATC astigmats versus astigmats corrected

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by Approved Laser B. And we can see that across the board, the ATC percentages are the lowest and more than meet the FDA guidelines.

[Slide.]

Here is a summary of the safety parameters. With the combined spherical and astigmatic cohorts, which is an "n" of 678, we had only .3 percent with a loss of more than 2 lines of best corrected vision. That's actually an extremely percentage, far under 1, and the Guidance Document says less than 5. We have one patient, or .2 percent, with best corrected vision worse than 20/40. This person has recovered to a preop level of 20/20 at 9 months. We have no cases where the haze after the 6-month visit was so bad that best corrected vision was lost and no cases of more than 2 diopters of induced astigmatism.

[Slide.]

If we look at corneal haze, most of our patients had none or a trace. We did have one astigmatic patient with 2-plus haze. This person has been retreated for regression and suffers no loss of best corrected vision.

We also had one person with 3-plus haze in the spherical cohort, and this person has recovered a mild haze at 9 months and has 20/20 best corrected vision.

[Slide.]

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If we look at intraocular pressure at 6 months, we have two astigmatic patients who had a pressure reading above 20, and we had one astigmatic patient who had an increase of greater than 10 millimeters of mercury. This person was 14 preop, had an IOP of 26 at 6 months, and last reported is back to 14.

[Slide.]

Complications reported at any time are listed on the left here, and you can see that in our spherical and astigmatic cohorts, the percentages are really very low.

[Slide.]

If we look at adverse reactions--and they are listed here on the left--the FDA guidance criteria say that we must have less than 1 percent for each individual category and less than 5 percent total. We certainly meet the total, less than 5 percent, very easily, and we meet the criteria for less than one percent in every category but corneal infiltrates.

Here you see in our primary cohort, "n" equals 678. We had a 1.6 percent incidence, and when we include all eyes with an "n" of 884, it's still 1.6 percent.

This became apparent to us that we had a higher-than-desirable infiltrate rate at about halfway through the study, and we studied it very seriously. We

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brought in two experts, Greg Schultz and Steve Wilson, experts on corneal healing, to pow-wow with us to look into the possible etiology. The leading contender before and still is contact lens-induced hypoxia.

Fonn, in his recent ARVO [ph] abstract found in 177 patients a 16.6 percent incidence of infiltrates in extended-wear soft lens wearers, uninjured, normal myopic eyes when this data was normalized to 3 months.

Let me also point out that this is the first PMA that comes before you where contact lens wear in the first week postop is a routine part of the protocol. All the other PMAs included bandaging. And even though that might not be part of their labeling, bandaging is not how it is done now. In the real world, everybody uses a bandage contact lens. So this does reflect what is being done in the real world, and we felt that contact lens hypoxia was the culprit.

[Slide.]

We also looked into the use of NSAIDs with concomitant steroids and the toxicity of multiple drops and preservatives that might be absorbed into the contact lenses. We also looked into the epithelial removal technique.

[Slide.]

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So the steps that we took to try to reduce our infiltrate rate halfway through the study were that we reduced the use and duration of NSAID drops; we switched to blade removal of epithelium instead of rotating brush; we allowed the doctors to pick the type of antibiotic and steroid combination that they wanted to use, and they were allowed to pick what type of bandage lens they wanted to use.

[Slide.]

So we really looked into the possible related factors with all of our cases. We looked at contact lens-wearing history, the range of correction, the age of the patient, the gender, the ablation time--all of the things you see here.

[Slide.]

We also looked at the type of bandage lens that was implicated in these infiltrates--here, you see them on the left--and the postoperative drug regimens that were implicated.

[Slide.]

We looked at the brush and blade question here, and we found that the incidence of infiltrates with brush and with blade were not statistically significantly different.

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[Slide.]

So we determined in the end that it was probably contact lens-induced hypoxia. But let me give you the details on these eyes with the corneal infiltrates. The last reported uncorrected vision is listed here for each patient, and you can see for the most part, they are excellent. There are two people with suboptimal uncorrected vision. One is 20/80. She was minus 650, is now minus 150, and is awaiting retreatment. There is another individual with worse than 20/200 vision. This person had an incomplete procedure which resulted in no refractive correction at all.

[Slide.]

There is one serious adverse reaction that occurred out of 884 patients, and I will tell you about him. He is a 35-year-old Caucasian, minus 3/minus .50 at 170. Everything went very well until postop day three, when the contact lens fell out, and the patient played tennis, with perspiration pouring from his forehead down into his eyes. He developed an infiltrate that was later positive for staph coag negative and alpha strep. The eye healed with the appropriate treatment, but he was left with a dense, 4.5 millimeter central haze. Between one and 3 months postop, his best corrected fluctuated, even though his hard lens

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refraction was 20/20.

[Slide.]

After a PTK performed with a VisX laser 5 months postop, the patient was exited from the study. He now has a best corrected of 20/20 and wears a plus 6 daily wear soft lens for his hyperopia. He is satisfied with his PTK results and his contact lens correction.

[Slide.]

We looked at patient satisfaction. Most of the patients were quite satisfied, but we had one extremely unsatisfied spherer--or, actually, excuse me--two patients, for an incidence of 0.6 percent. One was retreated, and one is 20/32 uncorrected. We had an incidence of 0.5 percent extremely unsatisfied astigmats, and this is one patient. this is a person who regressed from minus 8 to minus 4.5.

[Slide.]

As far as quality of vision, most patients were quite pleased. We had an incidence of 0.6 percent quality of vision significantly worse in our spherers. This represented two patients, one who was retreated, and the person I've already told you about who is actually 20/32 uncorrected.

[Slide.]

95.2 percent of our spherers and 93.4 percent of

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our astigmats never wear distance correction.

[Slide.]

We asked patients many questions about the quality of their vision--light sensitivity, headaches, double vision, pain and so on--and for our spherers and our astigmats, the incidence of these things being significantly worse was very low.

[Slide.]

But when we look at night driving difficulty, that is the one thing that stands out--4.3 percent of the spherers and 9.4 percent of the astigmats said night driving was significantly worse after the surgery. However, this compares favorably with Approved Laser B; when this exact question was asked, the incidence of significantly worse complaints was 4.8 percent for the spherers and 24.8 percent for the spherers and 25.9 percent for the astigmats.

[Slide.]

We retreated for undercorrection, regression and induced cylinder. The data was included in our primary cohort until they were exited for retreatment. Epithelial scraping, however, was performed only for overcorrection, and we included the data in the primary cohort before and after the scraping, and the follow-up continued as normal.

[Slide.]

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Our incidence of retreatment was 1.9 and 3.8 percent, respectively, for the spherers and the astigmats, and for epithelial scraping, it was 0.6 and 0.9 percent, respectively.

[Slide.]

If I tell you the last reported status on our laser retreatments, this also bucks the conventional wisdom, which is that retreatments do poorly. Here, you see the FDA guidance criteria once again for less than 7 diopters, and we can see that even the laser retreatments more than meet the uncorrected vision percentages for 20/40 or better uncorrected and plus or minus .5.

[Slide.]

We did subgroup studies. One, on contrast sensitivity, was performed with the MCT 8000 under four measurement conditions on 65 domestic eyes and 99 foreign eyes. Our results, which I will show you--we did see some changes, but they were not considered clinically relevant.

[Slide.]

Here, you see the foreign cohort, the Greek data, and this is contrast sensitivity collected under daytime conditions, night, simulated daytime with peripheral glare, and nighttime with central glare. Here, the spacial frequencies are represented in five colors, from white,

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which is 1.5 cycles per degree, to blue, which is 18 cycles per degree.

For the most part, these tall bars indicate patients with no change. Well, a few people did get better and worse in each set of circumstances, but we felt that the changes were not clinically relevant.

[Slide.]

When we look at our domestic cohort at 6 months, the results are exactly the same.

[Slide.]

The endothelial cell sub-study, we counted cells with a Konan non-contact specular microscope on 135 domestic and 90 foreign eyes, and we found no clinically significant changes in cell density from baseline.

[Slide.]

Here, you see the baseline. The Greek data is in green, the U.S. data in yellow. And all the changes are actually under 5 percent. So we say that there were no clinically significant changes.

[Slide.]

So in summary, for effectiveness, the ATC domestic data on uncorrected vision and dioptric accuracy exceed all criteria set by the FDA Guidance Document, exceed the results from lasers approved for a lower range of

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correction, and are stable at 3 months.

[Slide.]

As far as safety, the best corrected vision and induced cylinder are within the limits of the FDA Guidance Document. The incidence of adverse reactions are lower than the permitted, except for infiltrates which healed without sequelae. With subgroup analyses, there were no clinically relevant effects on contrast sensitivity or endothelial cell density.

Thank you.

DR. HIGGINBOTHAM: You still have 15 minutes.

DR. GAUTHIER: Thank you.

I am Charline Gauthier, and I am the Director of Clinical Affairs--

DR. HIGGINBOTHAM: Excuse me. Dr. Rosenthal?

DR. ROSENTHAL: Am I allowed to interrupt now?

DR. HIGGINBOTHAM: No.

DR. ROSENTHAL: Okay.

[Laughter.]

DR. GAUTHIER: I will be presenting the responses to the reviewers' questions which we received in the week or two prior to this Panel meeting.

[Slide.]

The first question actually was posed to the Panel

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by Dr. Eydelman, our FDA reviewer, and it was with regard to the follow-up of eyes treated and whether or not the astigmatic group had enough follow-up to provide reasonable assurance of safety and effectiveness.

[Slide.]

On January 23, we submitted to you what we are calling supplemental data, and this data included 9-month follow-up on over 100 eyes in the astigmatic group. What we see here is a summary of the visual acuity results, and at 6 months, where we presented all the results to you, we see that we have 91 percent of these patients 20/40 or better, 78.3 percent 20/25 or better, and 56 percent 20/20 or better.

[Slide.]

On the slide that shows the refractive accuracy, again, we have 9-month follow-up data on over 100 eyes, and we see here that at 6 months, we have 72 percent within a half and 89.9 percent within 1 diopter.

[Slide.]

So we do have now 9-month data on the astigmatic group, and these data are further supported by our spherical cohort, which show 12-month data on, again, over 100 eyes. And I won't review the data here, because you have it in front of you, but you can see that the uncorrected visual

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acuity is very stable after the 3-month visit, as is the refractive accuracy on the next slide--again, from 3 months to 12 months, with 144 eyes at 12 months in the spherical primary cohort.

[Slide.]

The next question was regarding the moderate myopes and whether there was adequate data on the moderate myopes to support safety and effectiveness.

[Slide.]

Again, in the January submission, we submitted some additional data on these patients. There was a little confusion as to why the sample size changed from our November submission to our January submission, and I would like to explain why that was.

In November, we submitted 6-month data on 30 spherical eyes in the primary cohort and 40 astigmatic eyes, for a total of 70 eyes out of the 79 enrolled eyes here. In January, we combined our spherical and astigmatic primary cohorts--so that would be the entire 79 eyes--and we have 6-month follow-up on an additional 8 eyes that have been treated in the "continuing cases" cohort. So we have 87 total eyes that range in dioptric correction between 7 and 10 diopters.

[Slide.]

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If we compare this sample size to other approved devices, we see that the 87 we have compares very favorably to the 84 eyes that were presented by Approved Laser B and given approval for the entire range of astigmatism up to 6 sphere and 4 cylinder.

If we break out the moderate myopia group into stratified dioptric ranges from 8 to 8.9 and 9 to 10, we have 24 eyes between 8 to 8.9 and 11 eyes between 9 to 10. Again, this compares very favorably to the 6 eyes that were presented by the LASIK group about 6 months ago between the range of 14 to 14.99, and an approvable status was given.

[Slide.]

Here is the data on that moderate myopic group that you were given in January. At 6 months, we see that 86 percent of these eyes are 20/40 or better.

[Slide.]

Refractively, at 6 months, we have 80 percent within 1 and 54 percent within .5 diopter of target correction.

[Slide.]

If we break the groups up, we see here that 7 to 7.9, 8 to 8.9 and 9 to 10, with the FDA guidance for lower myopes here, we meet the guidance for 20/40 or better for two of the groups, slightly below in our 8 to 8.9 group, and

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again we exceed the 20/40 or better that was presented by the approvable LASIK PMA 6 months ago.

[Slide.]

If we look at all the key safety and effectiveness parameters, the FDA guidance listed here, we see that we meet all of those guidance requirements, including the safety requirements which, for a loss of greater than 2 lines of BCVA, the requirement is less than 5 percent, and we have 3.4 percent, and we have one eye that is 20/40 or worse.

Again, there was some concern by the panel reviewers on the loss of best corrected VA, and I'd like to go over the three eyes in the moderate myopic group that actually had that loss and tell you what happened to those eyes.

The first eye was 20/20 or better preop, at 6 months was 20/50, and at 10 months has resolved to 20/20. The second eye was 20/12.5 preoperatively, went to 20/25, and at 7 months was 20/16. The third eye was 20/20 at preop and has been reduced to 20/40 and at 9 months still has 20/40 best corrected, because they are experiencing some haze and regression. So 2 out of the 3 eyes have improved to within one line of their preop best corrected VA.

[Slide.]

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So these moderate myopes that we have supplied to you meet the performance criteria in the FDA Guidance Document for low myopia, and we believe that the performance across the range justifies the approval to minus 10.

[Slide.]

The next question was regarding the patients in the range of 4 to 6 diopters of cylinder and whether or not there was adequate data on these patients.

[Slide.]

If we look at how common this correction is in the population, we see that less than 4 percent of eyes in the U.S. myopic population have between 4 and 6 diopters of cylinder. These eyes would, of course, include patients such as keratoconics, who would not have been included in our study.

Approved Laser B received approval up to 4 diopters of cylinder with 6 eyes in the range of 3.1 to 4 diopters, which is their highest range. Today, we have data to present on 4 eyes between the range of 4 to 6 diopters of cylinder.

[Slide.]

These 4 eyes will come from different parts of your PMA. Two of these eyes are in the primary cohort, 2 of these eyes were treated in the continuing cases cohort. You

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can see that we have between one and 6-month follow-up on these eyes, so not all the follow-up is 6 months. However, their best uncorrected VA at their last reported visit was 20/40 or better in all the eyes, and in 3 of the 4 eyes, beset corrected VA was improved from their preop level.

[Slide.]

So we know that these corrections are rare in the population. We have seen approval given on 6 eyes in the past on the highest range of astigmatism, and we feel that the uncorrected VA is good in these eyes and justifies approval.

[Slide.]

The next question was with regard to the low amounts of astigmatism, and one of the reviewers was concerned that the efficacy of the procedure was limited in the range of less than or equal to 1 diopter and felt there was residual cylinder. They also pointed out correctly that there was a discrepancy between two of our astigmatic tables. And again, I'd like to describe where that came from.

[Slide.]

There are FDA tables that were supplied to us to complete on axis shift, and those tables categorized the cylinder range as less than or equal to 1 diopter. The

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tables that are used in the remainder of our submission categorize low amounts of cylinder as less than 1. So that is the difference between those tables and why the sample sizes did not agree between those two tables.

[Slide.]

If we do look at the 41 eyes that were treated for either .50 or .75 diopters of cylinder, we find that none of these had residual cylinder of 1 diopter or more. If we look at the 8 eyes that the reviewer was concerned about, these 8 eyes had a preop cylinder of 1 diopter and had residual cylinder of 1 diopter or more postoperatively.

[Slide.]

This is how those 8 eyes turned out. Three of them had either no induced cylinder or .25 diopter of induced cylinder at 6 months; one eye had 1 diopter of induced cylinder, and at 9 months, that eye is now 1.25 diopters postoperatively, or has .25 diopter induced; and one eye had 1.25 diopters induced cylinder. This eye was treated 90 degrees off axis, and that was due to a calculation error when going from plus cylinder to minus cylinder form on the CRF.

That patient has recently been retreated for this amount of residual cylinder and is now plus .50 diopter sphere and 20/25.

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[Slide.]

If we look at the results of these low amounts of astigmatic correction, we see that the scalar reduction is 70 percent, which again compares favorably to the Approved Laser in this range, although theirs is up to 1, of 56 percent; our vector reduction is 89 percent; we have 20/20 or better in 69 percent of these eyes, again compared to 35 percent in Approved Laser B, and 86 percent are 20/40 or better.

[Slide.]

So the sponsor requests the approval of corrections less than 1 diopter of cylinder because we believe the data is supportive and is superior to prior approved laser results in this range.

[Slide.]

The next question was regarding the minimum age that the patient should be in order to be treated with the laser. One reviewer recommended 21 years of age. This recommendation was based on literature on refractive stability in young patients, and also, there has been a precedent set at previous Panel meetings where Approved Laser B had a restriction of 21 years for astigmatism. This was primarily due to pupil size in young patients being large, and the company was using a zone diameter which was

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quite small in their astigmatic treatment.

The youngest patient in this study was 24 years of age, but they were still granted 21-year minimum age. The same company had their spherical approval down to 18 years of age.

[Slide.]

We provided the Panel with data on 10 eyes of 8 patients between 19 and 21 years. The preop range was between minus 2.50 and minus 7.50. The last reported status on these eyes, which is also provided, is 90 percent of the eyes had 20/25 or better, and 80 percent were within .50 diopter of target. Two of these eyes were retreated, and one eye had a corneal infiltrate in the first postoperative week, but all 3 of those eyes have done very well.

[Slide.]

So the sponsor requests a minimum age of 18 as presently in our labeling, because the data was supportive in 19- to 21-year-olds even though we did not have an 18-year-old in the study, and we believe that our proposed labeling addresses the refractive stability in two ways. One is that it is required that refractive stability is shown for at least a year prior to surgery, and we also have the requirement that manifest and cycloplegic refraction must be in agreement. Our treatment zone for astigmatism is 5.5 by

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7.5, which reduces the concern about pupil size.

[Slide.]

The next question was regarding residual corneal thickness. This has been addressed at the Panel and at Eye Care Technology Forum before, as well as earlier this morning, about whether 200 or 250 microns residual is sufficient to avoid endothelial cell damage and ectasia.

[Slide.]

If we look at our theoretical minimum residual, we see that at 6 millimeter zone size for a spherical correction, our depth per diopter is 15 microns per diopter. This is slightly different from what you may have seen before, and that is because we don't use Monolin's formula, but our calculation is based on our specific shape profile.

For a minus 10 correction, then, our theoretical maximum depth would be 150 microns. If we have the minimum corneal thickness of 400 allowed in this study, with a 50 micron epithelial thickness, then our theoretical minimum residual is 200 microns of tissue. For the astigmatic group, it would be 217 because of the smaller zone size; there's a slightly less amount of tissue taken per diopter.

[Slide.]

So our current proposed labeling has the requirement of a minimum corneal thickness of 400 microns,

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and recently, we were made aware of a publication from Emery University to appear in the March AJO Journal, which was on 98 eyes treated for LASIK--these are human eyes--and they found no change in cell density at 2 or 12 weeks in treatments calculated to be between 208 and 340 microns from the endothelium. So this might be some data that would support the fact that 200 microns residual may be sufficient.

[Slide.]

One of the reviewers suggested a warning label for the minimum 7 millimeter pupil diameter that is required with our system in order to track. The reviewer suggested that there could be a potential significant adverse effect which might result if a pupil started to constrict during a procedure and this procedure was interrupted.

We do have currently in our "Operating Procedure" a minimum pupil diameter of 7 millimeters mentioned there. We have not had an occurrence of pupil constriction that resulted in an interrupted procedure after the ablation had begun.

We did present in the PMA data on 5 eyes that had a pupil constriction occur during mechanical epithelial removal. These eyes had to be redilated, and once they were redilated, the treatments were begun and completed

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successful--and the data again is in the PMA.

In addition to that, the software stores the location and the number of pulses that are fired at all time points, so that if the procedure is ever interrupted, you can start either the next minute or the next week at the same point that you left off at; this also guards against any problems in terms of restarting an interrupted procedure.

[Slide.]

So again, we believe that our current proposed labeling describes the requirement of 7 millimeter pupil dilation, and that safety mechanisms are in place to facilitate completion of interrupted procedures.

[Slide.]

One of the reviewers additionally asked for recommendation on overcorrection in parameters associated with overcorrection. They specifically mentioned humidity and temperature and asked a question as to whether or not longer ablation times were associated with overcorrections.

[Slide.]

The humidity range that we recommend in our operator's manual is 40 to 60 percent humidity, because we do find that at lower humidities, we had more overcorrections. Temperature was not related to

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overcorrection, but we have recommended 70 to 75 degrees. And epithelial removal time, again, we did find a correlation with longer epithelial removal times and more overcorrection, so we have always recommended a 2-minute target epithelial removal time.

In answer to the question, we did not find a correlation between overcorrection and ablation time; however, we did find that of our overcorrected eyes by cycloplegic refraction at 6 months, 73 percent of them were over 40 years of age, which correlates with our statistical finding that older patients tend to have more overcorrection.

[Slide.]

Finally, one of the reviewers asked about recoil pressure waves, and thought that there might be a greater recoil pressure wave over a smaller area with a scanning laser which could result in significant small-diameter pressure waves that might damage the corneal endothelium.

This was addressed in Section 4 of the PMA, and it is true that a smaller-diameter beam does cause slightly higher recoil pressure waves, but they are on the same order of magnitude as the wide beam systems. However, with small beams, the waves dissipate faster under the beam, and this was shown by Siano et al. in 1998, who compared a 1

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millimeter beam to a 3 millimeter beam and found that with the 1 millimeter beam, the waves dissipated very quickly.

If we were to see an effect of this, we would expect to see it in our clinical data on endothelial cell density and, as Dr. McDonald showed, we did not find a significant effect on endothelial cell density.

[Slide.]

I have been also asked to mention that corneal topography was measured both preoperatively and postoperatively in this study; however, it was not needed to clarify any of our complications or anomalous results.

This concludes our clinical presentation. We believe that the data we have presented provide assurance of safety and effectiveness of this device.

Thank you.

DR. HIGGINBOTHAM: Thank you. You have one minute to spare.

Dr. Rosenthal?

DR. ROSENTHAL: Thank you, Madam Chairman.

May I make a comment about what the Panel's charge is? The Panel's charge is to evaluate this device with regard to the data provided on this device in terms of safety and effectiveness.

If the company wants to use comparative data, they

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should have done a study in which they did comparative study. The information that the company provided with regard to comparisons was made by the company based upon their understanding of the data and has not been validated by the Food and Drug Administration.

Thank you.

DR. HIGGINBOTHAM: Thank you for that clarification.

The Panel has a decision to make--break now or break later. Let's break now. We will take a 10-minute break. It is now 2:58, so let's come back at 3:10.

[Recess.]

DR. HIGGINBOTHAM: AT this point in time, we'll have the FDA review, and I believe, Dr. Eydelman, you are proceeding at this point. The floor is yours.

DR. EYDELMAN: Thank you.

I would like to thank the sponsor for providing me with a copy of their presentation prior to this meeting, allowing me to avoid redundancy in my presentation. Today, I will therefore only highlight some points for Panel consideration and will not present a comprehensive review of the clinical studies in this PMA.

[Slide.]

Two features of the T-PRK system distinguish this

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technology from the currently approved excimer lasers. These are the small-diameter scanning beam and the eye-tracking system.

[Slide.]

The analysis of the impact of the small scanning beam on patient treatment has been reviewed by FDA staff. At present, there is no evidence for nor any theoretical hypothesis pointing to an increased risk associated with this technology.

Analysis of the eye-tracker effect brought to our attention the following. To engage the tracker and to optimize the tracker performance, it is necessary to achieve a minimum preoperative pupillary diameter of 7 millimeters in all potential subjects for this procedure.

As sponsor pointed out in their presentation, in the clinical study, 5 eyes had pupil constriction during mechanical epithelial removal, and all treatments were able to be completed successfully after redilation. Thus, pupillary constriction after initiation of epithelial removal doesn't appear to be problematic if redilation is achieved. However, future users should be aware of the minimum preoperative pupillary dilation of 7 millimeters, which is a unique subject inclusion criteria associated with this device.

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[Slide.]

The minimum required corneal thickness stated in the protocol in this study was 400 microns. As was pointed out in the sponsor's presentation, for an eye with a preoperative thickness of 400 microns undergoing maximum spherical ablation, the residual corneal thickness would be 200 microns. Since the current Guidance Document defines a minimum residual corneal thickness of 250 microns as a safety margin which precludes the need to track the ablation effect on the corneal endothelium, FDA was specifically interested in results of the eyes with residual corneal thickness of 200 to 250 microns.

Thus, the sponsor was asked to subdivide the endothelial cell sub-study results to analyze separately all eyes with residual corneal thickness of 200 to 250 microns.

In response, the sponsor researched their database and realized that none of the corrections performed in this investigation encroached on the 250 micron residual corneal thickness.

In light of these facts, the Panel will be asked for recommendation on appropriate labeling.

[Slide.]

As was already mentioned, the sponsor is asking approval for up to 6 diopters of cylinder. In the sponsor's

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presentation today, we have seen some of the results for eyes with a higher range of preoperative cylinder. This slide summarizes the number of eyes currently available with 6-month follow-up. As you can see, there are indeed 9 eyes with preoperative cylinder range of 3 to 6 diopters. However, 6-month data is only available on one eye with preoperative range of 4 to 6 diopters.

[Slide.]

Statistical analysis showed overcorrection to be associated with high attempted corrections, lower laser room humidity, and longer de-epithelialization times. These findings are important for the surgeons to be aware of, and they will be reflected in the labeling in addition to the currently-stated operating procedures.

[Slide.]

Now I would like to turn your attention to the questions.

Question Number 1: "Do the safety and effectiveness outcomes stratified by diopter of preoperative sphere and cylinder support approval for the full range of requested refractive indications of minus 1 to minus 10 diopters of sphere and less than or equal to minus 6 diopters of astigmatism? Is distinct labeling warranted for eyes with any preoperative refractive range?"

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Question Number 2: "The stability for astigmatic treatment with this device has been established in accordance with the FDA Guidance Document to occur between 3 and 6 months. This PMA contains full analysis of astigmatic 6 months data on 187 eyes and analysis of key safety and efficacy parameters for 112 eyes at 9 months. Currently, there is no 12 months data available for astigmatic treatment. Is the current follow-up of eyes treated sufficient to provide reasonable assurance of safety and effectiveness of this device for the treatment of astigmatism?"

Question Number 3: "The Guidance Document defines a minimum residual corneal thickness of 250 microns as the safety margin which precludes the need to measure the ablation effects on the corneal endothelium. None of the corrections performed in this study encroached on the 250 micron residual corneal thickness. However, with this device, minimum residual corneal thickness of 200 microns would be achieved with the preoperative corneal thickness of 400 allowed under the protocol."

"For the labeling, the sponsor is proposing to keep the entry requirement of 400 and add language which advises that for eyes with preoperative corneal thickness of 400 microns and corrections greater than 6.5 diopter

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spherical equivalent for spherical ablation, and 7.5 diopters spherical equivalent for astigmatic ablations, assessments of the effect on the corneal endothelium should be obtained with the use of endothelial microscopy."

" FDA is proposing the following warning label:

'Eyes with preoperative corneal thickness of 400 microns or less and corrections of greater than 6.5 diopters spherical equivalent for spherical ablations and 7.5 diopters spherical equivalent for astigmatic ablations should not be treated with this device due to the lack of data on the effect on the corneal endothelium.' What does the Panel feel is the appropriate labeling?"

And finally, Question Number 4: "Based upon 678 eyes treated in the U.S. clinical investigation together with the data from the foregoing study used as supporting evidence, has ATC provided reasonable assurance of safety and effectiveness of this device for the correction of low and moderate myopia with and without astigmatism?"

Thank you very much for your attention.

DR. HIGGINBOTHAM: Thank you for your concise presentation, Dr. Eydelman.

We have two primary reviewers. I have asked Dr. Mark Bullimore, MCOptom, Ph.D., to start the discussion.

Thank you.

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DR. BULLIMORE: Thank you, Madam Chairman.

Even though many of the questions that I raised have been addressed by Dr. Gauthier, I will cover them very briefly.

The sponsor is indeed to be congratulated on a well-executed series of studies and a very clearly-presented application, and particularly the accountability is most impressive.

As usual, Drs. Eydelman and Drum have made the task easier by their reviews, and my overall recommendation is that this PMA is approvable. However, I do have some comments regarding the conditions.

Regarding safety for both the spherical and astigmatic patients, the frequency of loss of best corrected visual acuity is low and within guidelines. Likewise, the adverse event rate is low and within the guidelines.

The primary cause for concern is the surprisingly high incidence of sterile corneal infiltrates. I regard this as having little long-term consequence. It may speak to the observational skills of the investigators, but I think it does need to be addressed in the labeling.

Regarding contrast sensitivity data, caution should be exercised when considering the results of some ATT tests, which is what we were presented with in the

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application, and if you are going to use T-tests in the future, I would encourage the FDA to lead sponsors toward either adjustment and promotable comparisons or some sort of analysis of variance. In summary, though, the contrast sensitivity data show no meaningful change.

Regarding efficacy, the spherical study portion of eyes reaching 20/40 or the various refraction benchmarks exceed guidelines and are thus acceptable.

Regarding the astigmatism study, I found the astigmatism data to be most impressive, as was summarized in one of the slides. On average, 79 percent of the intended cylinder correction was achieved. The advantage of vector analysis, as again demonstrated on the slides, is to allocate or determine the source of this shortfall. Since the mean intended vector, or the mean intended correction, was 1.42 diopters of cylinder and the achieved vector, that being the postoperative minus the preoperative, is 1.36, we can only attribute 4 percent of the shortfall to the laser. That means the remaining 17 percent is due to an error in axis alignment.

And as demonstrated by the sponsor, vector analysis indicates that the average error is 5 degrees, which of course agrees very well with the number I carry around in my head being the designated vector boy on the

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panel, which is 3 degrees axis error corresponds to a 10 percent reduction in the achieved correction, and that agrees very nicely with the data.

And this is impressively low given the potential sources of error in axis alignment, like refraction, alignment of the patient, laser, cyclophoria, et cetera.

My area of concern about the low astigmatic group has been dealt with very nicely by Dr. Gauthier, so I won't dwell on it.

Regarding the stability of refraction, this is excellent, and I have no further comments.

Regarding approvable range for spherical and cylinder, the sponsor has clearly presented adequate data to justify an approvable range up to 7 diopters spherical equivalent or however the data was presented. For higher degrees of myopia, I think it is prudent to pull the data for the spherical and astigmatism studies. This gives us a total of 79 patients in the 7 to 10 diopter range.

The proportion of eyes in this group losing 2 or more lines of best corrected visual acuity was 2.5 percent, that is, 2 out of 79. Of these 79 patients, over 60 percent, i.e., 48, fell in the 7 to 8 diopter bin, so I am comfortable extending the approvable range of 8 diopters and, depending on the pleasure of my colleagues on the

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Panel, would entertain extending it further. The labeling, however, should contain a warning to patients and practitioners about the increased risk of regression haze and loss of best corrected visual acuity for corrections above and beyond 7 diopters.

Regarding cylinder correction, I believe the sponsor has presented adequate data to justify an approvable range up to 3 diopters of cylinder. They have adequately addressed my concerns about the 0.75 and 0.50 diopter cylinders, so I have modified my recommendations accordingly.

Furthermore, given the size of the ablation area, the excellent efficacy, lack of safety concerns and informal comparison to alternative technologies and techniques, I would seriously consider extending the range to 4 diopters. Extending the range beyond 4 diopters does not appear to be justified.

Regarding labeling and other issues, I don't think that any other follow-up data or FDA analysis is necessary prior to approval. Unsubstantiated claims, however, if they are going to be included in the labeling, should be worded very carefully. For example, the theoretical benefits of the eye-tracking system presented by the sponsor are obvious, but they have not been demonstrated. This could

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only be achieved by means of a randomized clinical trial of the eye-tracking versus no eye-tracking.

As I have previously stated and as addressed by the sponsor, I prefer the age range to begin at 21 years, and I think concerns about endothelial loss are adequately addressed by one of the labeling options before us.

Finally, there is still need for a standardized questionnaire or instrument for the assessment of patient satisfaction concerning these refractive procedures. This would make interpretation of data from subsequent and different sponsors--their interpretation would then be much less hazard than it is at the moment.

I have one other comment which is not in my original review, and it is probably because I missed it. That concerns the use of postoperative steroids to titrate the refractive error. My colleagues on the Panel may regard that as a practice of medicine or optometry issue, but I would entertain some dialogue on that particular issue.

DR. HIGGINBOTHAM: We will get to that later.
Thank you.

Our other primary reviewer is Dr. James McCulley.
Dr. McCulley?

DR. McCULLEY: Thank you.

I too would like to compliment the sponsor on a

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well-designed and well-done study, and I am going to deviate for just a moment from my written presentation.

I think your comparisons to Approved Laser A, Approved Laser B, and especially to the approvable recommendation, quite honestly--whether it is appropriate or not, I am not sure--but to me, it detracted from your presentation. I think you made an excellent presentation. I think those comparisons--for reasons that I am going to have to think about more--I found bothersome, and they honestly detracted from your presentation. They will not influence my opinion positively or negatively, even though I did find them bothersome.

My overall impression of the PMA is that it is approvable. I think the range of correction requested by the sponsor, however, is not justifiable or supported by the data, and in actual fact, my recommendation is 1 to 7.99 for sphere and 1 to 4.00 for astigmatism.

The 8.00 to 10.00, I might be swayed there, maybe. There were 21 eyes at 6 months between 8 and 9 diopters, 10 eyes between 9 and 10, but the numbers are small, so you are hurt very badly by 2 eyes that were less than 20/40 from a percentage standpoint, one eye less than 20/40 in the 9 to 10, 2 in the 8 to 9. So the percentages are very bad because the numbers are low.

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So I am not so sure about the 8 and 10. Up to 8, I am comfortable; up to 4 diopters of astigmatism, I am also comfortable.

The stability of the astigmatic correction, I am very comfortable with. That was an issue raised. The entry requirement of the 400 microns, I can live with, but we still have an issue about that 200-250, not just endothelium, and we are beginning to see that we may not have to worry about the endothelium if we stay 200 microns away from it, but we still do not know about the structural integrity, and until we know that, I am uncomfortable supporting any labeling that would state anything other than that the posterior 250 microns of the cornea should not be disturbed.

And the last question the FDA brought up was did it support assurance of safety and efficacy, and yes, with the limitations that I had.

There were some other questions in the FDA clinical reviews that were not addressed in the questions to the Panel, and I want to go through those very quickly. One relates to the pupillary diameter of 7 millimeters and that that must be maintained during treatment. I think this clearly needs to be stressed with a warning in the labeling that a minimum of 7 millimeter pupillary diameter must be

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established and maintained throughout. If you have gotten very far through the epithelium and have the pupillary constrict, you still potentially have corneal hydration problems. So I think this is something that there needs to be ample warning about. There are potentials for significant adverse events if that occurs at an inopportune time.

The incidence of the presumed-to-be-sterile infiltrates in the corneal stroma is bothersome. I think that you have dealt with that to a satisfactory degree as far as I am concerned, but I think there needs to be a warning in the labeling until there is further resolution of that. I am still a little bit puzzled by that, as I gather you probably are to a degree, too. As was pointed out, it is the standard to use a bandage lens. My impression is that that degree of sterile infiltrates is not what I would be expecting to see or have seen. But I think you deal with it reasonably well and it should not interfere with the recommendation for approvable.

The parameters associated with overcorrection should be clearly stated in the labeling. I think that the room humidity and temperature issues, especially considering that at one location at one time, the laser had a false gas alarm and shut the laser down, that was attributable to

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temperature, that you should have clear humidity and temperature ranges that should be maintained with instructions to maintain both temperature and humidity within those ranges by whatever mechanism is required, depending on the climate.

The issue of 19 versus 21--there is data on one patient 19 years of age, 4 who are 20. I just don't see the data there to support approval of anyone less than 21 years of age. I think there does need to be a warning in the labeling about the underestimation of central corneal intraocular pressure taken by Goldman [ph] applanation tonometry [ph]. Peripheral Goldman is accurate, as is, apparently, pneumotonometry, either centrally or peripherally, but certainly a warning about the central Goldman applanation tension underestimating should be in the labeling.

You addressed one of my questions as a non-engineer which was an engineering question, effectively in your presentation. The one that I am not certain about is that measured removal of corneal tissue to achieve a one-diopter change with a 6-millimeter optical zone has been less than 15 diopters. I am a little bit--and this is just a curiosity point for me--why is it that you are removing 15 microns of tissue to achieve a one-diopter change with a 6

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millimeter zone?

DR. HIGGINBOTHAM: Is that the completion of your review?

DR. McCULLEY: The last comment I have--I have two kind of editorial comments. One is that you had less good outcome with RGP lenses in your study. I think this can extrapolate to impacting previous discussions about how long a person must be out of their contact lenses before they are treated, and that one must absolutely ensure that the cornea has recovered its normal curvature, or its natural, native curvature, prior to treatment. And cutting corners on this for marketplace purposes, you have data now that suggest that that is not a good idea.

And the last comment is that no topographic information was entered into the review of this application by the FDA, and we have had difficulty in the past determining the role of topography in assessing other PMAs, and I guess my question is are we giving up on topography as a useful clinical tool in assessing safety and efficacy in laser keratorefractive surgery. I suppose that is more of a question to the FDA, but I stuck it in here.

That completes my review. I recommend approvable, with the range of 1 to 8 spherical correction and 1 to 4 astigmatism--or, up to 4 astigmatism--sorry. I misstated

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that.

DR. HIGGINBOTHAM: Thank you, Dr. McCulley.

I'd like to invite the sponsor to come back to the table and entertain questions from the Panel. And since you, Dr. McCulley, had a question within your review, you can lead off.

DR. McCULLEY: Oh, yes--why do you guys have to remove 15 microns, or do you, or is that just a calculation, or are previous calculations and measurements inaccurate? How can you resolve that for me?

DR. HIGGINBOTHAM: Please identify yourself.

MR. FREY: Randy Frey. The 15 micron is a calculation. It is based on the nature of the shape that we are making to the cornea. The only thing I can shed light on is if you look over the range of excimer technology, one would find that using topography, in fact, one role of topography has been to show the effect of ablation diameter, and we feel that we have achieved relatively wide ablation diameter, and the only reason you can have a smaller or a larger has to do with the actual shape you put on the eye. So the approximation under the Monolin formula has never really proved in practice based on the topographic analysis, and when we made the assessment starting with a nominal 43 diopter corneal curvature and looked at straight spherical

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correction, our algorithm turns out to be approximately 15 microns per diopter.

DR. HIGGINBOTHAM: Okay. Any other questions from the Panel?

Dr. Macsai?

DR. MACSAI: I was wondering if the sponsor could address the difference in results between the genders found. Should I just list my questions, or--

DR. HIGGINBOTHAM: We can take them one at a time. Does the sponsor have an answer?

MS. GAUTHIER: Yes.

DR. HIGGINBOTHAM: Okay. Please identify yourself.

MS. GAUTHIER: Charline Gauthier, Autonomous Technologies.

We looked extensively at this question as well, about the gender difference we found in the spherical cohort, that males did better than females, and we'll see if my answer here will suffice; if not, I can show you some further overheads.

When we analyzed it in detail, we not only looked at Patient A in terms of the females, but we also looked the use of hormones, and we found that the group of women over the age of 40 using hormone replacement therapy actually had

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significantly worse results than any other group, and that likely pulled down our female rules. And that has been shown in literature as well, previously, in PRK.

So our only explanation would be that combination. Other than that, we really didn't find anything in terms of the age range of the different gender groups.

DR. HIGGINBOTHAM: Dr. McCulley?

DR. McCULLEY: In follow-up to that, you associated it with older women on hormone replacement therapy. Was there a consistent finding in that group that was different that would then allow you, or allow one, to adjust one's approach or algorithm to avoid those poor results?

MS. GAUTHIER: Again, Charline Gauthier. We don't believe that a change in the algorithm would affect the results, because we didn't find that refractively, they had a different result; just not as many of them saw 20/20. Now, whether that has to do with tear film or stoma edema, I don't know. But the refractive results were similar; it was the visual acuity results that were different between the genders, and that is where the difference showed up with the older patients and certainly older women on hormone replacement therapy compared to those who were not.

DR. McCULLEY: So what you are saying, though, is

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that you don't have an explanation for why their vision was decreased.

MS. GAUTHIER: Exactly.

DR. McCULLEY: That would be interesting to know.

DR. HIGGINBOTHAM: Dr. Macsai and then Dr. Bullimore.

DR. MACSAI: Don't you think that this is a labeling issue--you, being Autonomous Technologies as a general--anyone can answer.

MS. McGARVEY: This is Shirley McGarvey, the regulatory consultant to Autonomous Technologies.

The data that we have and the manner in which we have stratified it does give us a difference with respect to older women on hormone therapy. The performance of that particular subgroup, however, is still consistent with and somewhat superior to results for the total population of prior approved lasers.

DR. MACSAI: I didn't ask you to compare to prior approved lasers--excuse me.

MS. McGARVEY: I understand. But if we would want to put this on the label, I think it is very useful information to put into the label. I think that if it is going to be a requirement in the label, it should be a requirement for all laser sponsors.

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DR. HIGGINBOTHAM: Dr. Bullimore?

DR. BULLIMORE: I think my comment has been adequately addressed by Dr. Macsai.

DR. HIGGINBOTHAM: Thank you.

Dr. Pulido?

DR. PULIDO: I first would like to commend the authors of this proposal for doing a wonderful job. It is very readable for me and made it easy to go through and understand.

What I would like to have you address for my clarification is considering the small numbers of patients who were more myopic, that were 8 or higher in myopia, and the small number of patients who had high cylinder, why do you think you are justified in having these as part of the indication?

MS. GAUTHIER: Charline Gauthier from Autonomous.

As I presented in my presentation, we believe that, yes, the numbers, certainly in the highest category being 11 eyes between 9 and 10, but 24 between 8 and 9--we thought, even with those small numbers, the results are acceptable and in fact exceed the Guidance Document. So that we believe that these patients are rare in the population, more difficult to find. We did enroll sequentially, so we couldn't pick the minus 10's as opposed

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to the minus 4's, and we closed our enrollment with what we had.

But we believe that the performance of the product is good, and we don't see any reason for a safety concern or an effectiveness concern in those eyes that is greater than what is required in the Guidance Document for low myopes.

The same argument, I guess, would be true for the high astigmats. Dr. McDonald showed that we didn't see a decrease in performance as we went across the ranges of astigmatism, and we feel that in the higher ranges of astigmatism, the system also seems to perform well, and that was shown by vector analysis, that the algorithm does correct the high amounts of cylinder just as well as the lower amounts. So again, although there are few patients in those categories, the numbers that are there show consistent performance with the lower dioptric ranges. And again, they are rare in the population.

DR. HIGGINBOTHAM: Thank you.

Dr. Macsai?

DR. MACSAI: This question is for everyone but probably Dr. McDonald. In the patients who have these corneal infiltrates, some of them were in Acuvue and a bunch of different kinds of contact lenses, and at the beginning of your presentation you spoke about the Protek lens being

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part of the protocol. So I am a little bit confused--did these patients get started in Proteks, and then they didn't fit, or moved, or fell out and got switched, or what happened?

DR. McDONALD: This is Marguerite McDonald speaking.

According to the original protocol, every patient got a Protek lens. About halfway through the study, we realized that our incidence was climbing above the 1 percent level, so we had a pow-wow to discuss what to do. One of the steps we took, just in case it was related to the Protek lens, was to let each investigator choose which bandage lens to use. So that is why--the first half of the study, everybody got Protek, and after that, some people stayed with Protek, a lot of people switched--Sureview, Acuvue--it was all over. And we continued to find the same incidence of infiltrates with all the new lenses being used.

DR. MACSAI: Okay. I didn't understand that. Thank you for clarifying it.

I have one other question. You talked about a patient who, after epithelial removal, the pupil became small, and the patient was redilated, and then the procedure was completed. I was just curious--I would have expected stromal hydration with dilation post-epithelial removal and

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a change in the results. How did that patient do?

DR. McDONALD: Marguerite McDonald.

Actually, that occurred five times, as I recall, and the patients did quite well. What I did when it happened to me was ask them to close their eyes, realizing that that is not perfect, but just to keep their eyes closed until we initiated again, and the results were very good.

MS. GAUTHIER: Charline Gauthier, from Autonomous.

I can give you actual VA results if you'd like. Four of those patients were 20/20 or better uncorrected in the follow-up--it's in your PMA in Section 3.4--and the follow-up was anywhere from 6 months to 18 months. One patient was 20/80, and that was an eye corrected for monovision, so that's why the uncorrected. But best corrected visual acuity was not affected.

DR. HIGGINBOTHAM: Thank you.

Any other questions from the Panel? Dr. Pulido?

DR. PULIDO: This is to Charline Gauthier again. In Table 2D of the submission dated January 23, there are 31 patients, then, who were myopes between 8 to 10, and loss of greater than 2 lines best corrected visual acuity was around 9 percent. Now, granted, these are small numbers, but rather significant.

MS. GAUTHIER: Charline Gauthier, Autonomous.

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Those are the 3 eyes that I detailed in my presentation. Two of those eyes have improved at their subsequent follow-up visits. One went from 20/20 and then came back to 20/20. One started at 20/12.5 and came back to 20/16. So we have one eye that still is 20/40 from a preop of 20/20.

You are right, the percentages are because of the small n's, but it does represent 3 eyes, 2 of which have improved.

DR. HIGGINBOTHAM: Dr. Jurkus?

DR. JURKUS: In your protocol, you have indicated on your patient selection that people who have worn PNNA or RGP lenses are required to have two examinations conducted 2 to 3 weeks apart which show stability of refraction without lens wear. I was wondering how many patients were actually not showing stability at 2 to 3 weeks and if any of them were included and if there was any difference in results for the RGP people.

MS. GAUTHIER: I'll speak first, and then Dr. McDonald might want to comment. If they were not stable after 2 to 3 weeks, they had to wait another 2 to 3 weeks; so they were not allowed in until that stability was reached.

DR. JURKUS: And how many subjects fell into that

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category?

MS. GAUTHIER: Who had to wait another 2 or 3 weeks?

DR. JURKUS: Yes.

MS. GAUTHIER: I am not sure at this time how many of those we had. We'll have to look that data up.

DR. McDONALD: Marguerite McDonald.

In my cohort, I can remember only one, and we made this individual go another 3 weeks, and that person had an excellent outcome.

DR. JURKUS: Did these subjects wear no contact lenses at all, or was it not RGP lenses?

DR. McDONALD: We were talking about RGP wearers--McDonald here--RGP wearers.

DR. JURKUS: But they didn't wear a soft lens during that stabilization--

DR. McDONALD: No, no. They wore nothing; they wore spectacles only.

DR. HIGGINBOTHAM: thank you.

Are there any other questions from the panel?

[No response.]

DR. HIGGINBOTHAM: Thank you, sponsor. You will be invited back two-thirds into the questions.

Now, Panel, we can deliberate. And I suppose at

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this time, we can take each question in turn, and I will ask Ms. Thornton to actually review each question.

Thank you.

MS. THORNTON: I can either read them, Malvina, or you can put them up.

DR. HIGGINBOTHAM: Either Ms. Thornton or Dr. Eydelman; either one.

DR. EYDELMAN: You can read them; I'll put them up.

DR. HIGGINBOTHAM: Okay.

MS. THORNTON: It will be a team effort here.

[Slide.]

Question Number 1. "Do the safety and effectiveness outcomes stratified by diopter of preoperative sphere and cylinder support approval for the full range of requested refractive indication of 1.00 to 10.00 diopters of sphere and less than or equal to 6.00 diopters of astigmatism?"

Do you want to take just the one part?

DR. HIGGINBOTHAM: Why don't you go ahead and finish it.

MS. THORNTON: Okay. "Is distinct labeling warranted for eyes with any preoperative refractive range?"

DR. HIGGINBOTHAM: I'll ask Dr. Bullimore to

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respond and then Dr. McCulley.

DR. BULLIMORE: I'll reiterate my previous statement. I think we can justify it to 8 diopters of sphere and 4 diopters of astigmatism, but I can be pushed either way; and I do think distinct labeling is warranted for eyes above 7 diopters regardless of the approved range.

DR. HIGGINBOTHAM: Dr. McCulley?

DR. McCULLEY: I am very comfortable with up to 8 for sphere, 1 to 8, and up to 4 with astigmatism. I don't think there is data there on the astigmatism for sure, and I'm not sure I would change my view there, because I would need something to change it.

And in the 8 to 10 range, I just don't quite see the kinds of numbers there that I would be most comfortable with, but I suppose I wouldn't throw a fit if that were the minority view and the majority of the Panel members felt otherwise.

DR. HIGGINBOTHAM: Are there any Panel members who would like to comment on this question?

Dr. Sugar?

DR. SUGAR: I agree. I just don't understand what "distinct labeling" means.

DR. HIGGINBOTHAM: Malvina, do you want to clarify?

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DR. EYDELMAN: Certainly. What we are trying to ask is if, in your opinion, any subgroup of the data, i.e., any specific preoperative range of refraction, requires warning or contraindication statement.

DR. McCULLEY: Thank you.

DR. HIGGINBOTHAM: Any other comments?

Yes, Dr. Yaross?

DR. YAROSS: Marcia Yaross.

Just a comment on the comparisons that were made previously. While it is clear that comparative claims cannot come from comparisons with other PMAs, for the purposes of benchmarking, sponsors have sometimes used issues of other PMAs in terms of amounts of data that have been required for approval in the interest of a level playing field.

So from that standpoint, perhaps some consideration can be made to the quantity of data from a level playing field consideration.

DR. HIGGINBOTHAM: Okay. Dr. McCulley and then Dr. Bullimore.

DR. McCULLEY: Well, I'm not sure that we have adequate assessment of this. One of the comments that was made pointed out a number of eyes in a certain refractive range for another study, but that in context, there were

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also some international eyes that entered into that deliberation. So I think that here, it is based on--for our purposes, I think we have got to look at this data, and I am comfortable up to 8 sphere and 4 cylinder.

DR. HIGGINBOTHAM: Dr. Bullimore?

DR. BULLIMORE: I think Dr. Yaross raises an important point. The only consistency in any of those approval processes or applications or whatever is the FDA. The personnel may have changed on this panel, and individuals might have different preferences, and indeed, those of us who may have sat on previous panels may not have voted for approval of those particular protocols. So I take the point, but I don't think we should be governed or handcuffed by history.

DR. HIGGINBOTHAM: Any other comment,

Dr. Yaross?

DR. YAROSS: No. Thank you.

DR. HIGGINBOTHAM: Okay. Any other comments regarding this particular question?

Malvina?

DR. EYDELMAN: I'm sorry. If I could just clarify Dr. McCulley's recommendation. Is it up to 8 sphere or up to 8 spherical equivalent?

DR. HIGGINBOTHAM: Dr. McCulley?

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DR. McCULLEY: It was up to 8 sphere and 4 astigmatism. I believe that's correct.

DR. EYDELMAN: Thank you.

DR. BULLIMORE: That's minus 8 with a minus 4 on top of it? I get confused when people want to use minus and plus cylinder.

DR. HIGGINBOTHAM: Do you agree, Dr. Bullimore, minus 8?

DR. BULLIMORE: That's fine.

DR. HIGGINBOTHAM: Sphere.

DR. BULLIMORE: Sphere.

DR. HIGGINBOTHAM: Okay.

DR. BULLIMORE: Just a point of clarification. In Table 2D, is this sphere or spherical equivalent?

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: I believe it is spherical equivalent. I don't have it in front of me; I would have to refer back to the slide.

DR. McCULLEY: If it's spherical equivalent, then my recommendation is spherical equivalent.

DR. HIGGINBOTHAM: Can we get some clarification on this table?

Dr. Eydelman?

DR. EYDELMAN: May I ask the sponsors? They have

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the table pulled.

DR. HIGGINBOTHAM: Yes.

MS. GAUTHIER: Yes, that's spherical equivalent range.

DR. EYDELMAN: I just wanted that clarification.

DR. HIGGINBOTHAM: Okay. So is it, then, minus 8 spherical equivalent, Dr. McCulley?

DR. McCULLEY: Dr. Bullimore?

DR. BULLIMORE: Let me look through the original documentation.

DR. PULIDO: Time out; I agree. I think we need--

DR. HIGGINBOTHAM: Dr. Pulido?

DR. PULIDO: Thank you, Dr. Higginbotham.

I'd like to take a little time to look, also, and see how their data is arranged, then.

DR. HIGGINBOTHAM: Is it possible to have this table projected so everyone is looking at the same information?

DR. McCULLEY: If this is what we are basing our decision on, if this was spherical equivalent, then it would seem to follow simply that it would be spherical equivalent.

DR. HIGGINBOTHAM: Is there anyone on the Panel who wishes to disagree with that comment?

Dr. Bullimore?

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DR. BULLIMORE: Since I was the person who suggested we merge the spherical and astigmatism data, I'm just trying to dig myself out of the hole in which I have placed myself.

DR. HIGGINBOTHAM: I gather that there is a desire to look at this information a little bit more closely.

Dr. Sugar, did you have a comment?

DR. SUGAR: No.

DR. HIGGINBOTHAM: If it's okay with the Panel, I would suggest that we move on to Number 2 and then come back to Number 1.

Dr. McCulley?

DR. McCULLEY: Could I suggest we leave that issue to be dug out by the FDA to see where the data is, whether it's sphere or spherical equivalent--

DR. BULLIMORE: I'm happy with that.

DR. McCULLEY: --because we're running around here like chickens with our heads cut off, and if we do have a consensus that it is 8 sphere or spherical equivalent and 4 diopters of astigmatism, that we state that consensus.

DR. HIGGINBOTHAM: Okay. Does everyone agree with that proposal? Okay. Let's proceed to Number 2.

MS. THORNTON: "The stability for astigmatic treatment with this device has been established in

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accordance with the FDA Guidance Document to occur between 3 and 6 months. This PMA contains full analysis of astigmatic 6 months data on 187 eyes and analysis of key safety and efficacy parameters for 112 eyes at 9 months. Currently, there is no 12 months data available for astigmatic treatment. Is the current follow-up of eyes treated sufficient to provide reasonable assurance of safety and effectiveness of this device for the treatment of astigmatism?"

DR. HIGGINBOTHAM: Dr. McCulley, then Dr. Bullimore.

DR. McCULLEY: Yes.

DR. HIGGINBOTHAM: Dr. Bullimore?

DR. BULLIMORE: Yes.

DR. HIGGINBOTHAM: Are there any noes on the panel?

[No response.]

DR. HIGGINBOTHAM: Okay. Let's proceed to Question Number 3.

MS. THORNTON: "The Guidance Document defines a minimum residual corneal thickness of 250 microns as the safety margin which precludes the need to measure the ablation effects on the corneal endothelium. None of the corrections performed in this study encroached on the 250

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micron residual corneal thickness. However, with this device, minimum residual corneal thickness of 200 microns would be achieved with the preoperative corneal thickness of 400 microns allowed under the protocol."

"For the labeling, the sponsor is proposing to keep the entry requirements of 400 and add language which advises that for eyes with preoperative corneal thickness of 400 microns and corrections of greater than minus 6.5 diopters SE for spherical ablations and minus 7.5 diopters SE for astigmatic ablations, assessments of the effect on the corneal endothelium should be obtained with the use of endothelial microscopy. FDA is proposing the following warning label: 'Eyes with preoperative thickness of 400 microns or less and corrections of greater than minus 6.5 diopters SE for spherical ablations and minus 7.5 diopters SE for astigmatic ablations should not be treated with this device due to the lack of data on the effect on the corneal endothelium.' What does the Panel feel is the appropriate labeling?"

DR. HIGGINBOTHAM: Dr. Macsai?

DR. MACSAI: The question here, I believe to be twofold--not only the effect on the endothelium, but corneal stability at 200 microns, because we are not talking about getting within 200 microns of the endothelium and then

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putting a flap back down, as we were this morning. We're talking about ablating to 200 microns. So I think there are two issues here.

In addition, I am kind of not sure how many 400 micron corneas exist that are normal. I don't know--maybe someone can educate me about that. I don't think that is considered normal.

DR. HIGGINBOTHAM: Dr. McCulley?

DR. McCULLEY: I'm not sure about that, either. But the point to me is that based on the information we have, not only--comfortable information about endothelium down to 200--but we don't have the structural integrity information. And I think the labeling, however, this is done, should state that the posterior 250 microns to the corneal stroma is not invaded, period. That is one issue.

The second issue about whether a 400 micron normal cornea could be entered or not, I'm not sure if, way out there on the tail of that bell-shaped curve, there are normal 400 micron corneas. I would wonder about it. I don't know that I have ever seen one.

DR. MACSAI: There are very few.

DR. McCULLEY: Oh, I have--in rabbits, but not in humans.

DR. HIGGINBOTHAM: Are you speaking in favor of

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the current wording--proposed?

DR. McCULLEY: No. The wording that I would propose--I'm not sure about what to say about the entry level for corneal thickness. The issue here, as far as I am concerned, is that any treatment should not be undertaken that will invade the posterior 250 microns of the corneal stroma, period.

DR. HIGGINBOTHAM: Dr. Bullimore?

DR. BULLIMORE: I agree with that. I can get behind that.

DR. HIGGINBOTHAM: Okay. Dr. Macsai?

DR. MACSAI: Well, I would still be uncomfortable enrolling a 400 micron cornea in this study--or, I mean, to be used with this laser. They didn't have any patients enrolled who were 400 microns. Personally, I have only seen it in patients with keratoglobus and keratoconus, or corneal ectasia or thinning disorders. So I have concerns about that number, 400 microns.

DR. HIGGINBOTHAM: Dr. McCulley?

DR. McCULLEY: My specific recommendation would not state a 400 micron cornea would be allowed. It doesn't address that point.

DR. MACSAI: Well, you see, it could be--

DR. HIGGINBOTHAM: Dr. Macsai?

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DR. MACSAI: --excuse me--it could be if you were doing just a 100 micron ablation on someone who had 400 micron preop, and it would still end u 300 microns. So I think we need to reword both the entry criterion and the safety cutoff of 250 microns.

DR. HIGGINBOTHAM: Is that your proposal, then?

DR. MACSAI: Well, my proposal would be instead of 400--but I would ask the sponsors if they have data, because there may be data I'm not aware of about 400 microns, and they probably have it.

DR. HIGGINBOTHAM: Dr. Pulido?

DR. PULIDO; Just a point of clarification for me from the cornea specialists on the Panel. If you have a 400 micron cornea and you ablate it down to 300 microns, is there less stability than taking a cornea that was 500 microns down to 300 microns?

DR. HIGGINBOTHAM: Dr. McCulley?

DR. McCULLEY: We don't know. I think that in other inclusion/exclusion criteria, we deal with the cornea being normal, and not keratoconus with or without ectasia or so forth, and that we don't set an entry level for minimal corneal thickness; that we leave that unaddressed by number.

DR. HIGGINBOTHAM: Any other comments on this question or issue?

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[No response.]

DR. HIGGINBOTHAM: I would like to invite the sponsor to make any--excuse me--

DR. ROSENTHAL: May I suggest you go through the fourth question? Since there are so few questions, maybe they could do all four together.

DR. HIGGINBOTHAM: Okay. I was instructed to do two-thirds, so this is three-quarters.

DR. ROSENTHAL: Okay. You have already passed two-thirds, Dr. Higginbotham.

DR. HIGGINBOTHAM: Okay. Whatever pleases you, Dr. Rosenthal. I'll be happy to do that.

The fourth question, please.

MS. THORNTON: "Based upon 678 eyes treated in the U.S. clinical investigations together with the data from the foreign study (102 eyes) used as supporting evidence, has ATC provided reasonable assurance of safety and effectiveness of this device for the correction of low and moderate myopia with and without astigmatism?"

DR. HIGGINBOTHAM: Dr. McCulley?

DR. McCULLEY: Yes, with the previous stipulations that have been stated.

DR. HIGGINBOTHAM: Would you like to restate that?

DR. McCULLEY: Up to 1 to 8 diopters of spherical

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equivalent and up to 4 diopters of astigmatism being the range, with the statement that no treatment be undertaken that would invade the posterior 250 microns of the corneal stroma.

DR. HIGGINBOTHAM: Dr. Bullimore?

DR. BULLIMORE: Hear, hear.

DR. HIGGINBOTHAM: Dr. Pulido?

DR. PULIDO: I agree.

DR. HIGGINBOTHAM: Dr. Macsai?

DR. MACSAI: As long as the corneas are normal on entry, I agree.

DR. McCULLEY: That's understood.

DR. HIGGINBOTHAM: Okay. And now, I would like to invite the sponsor to make any comments. I would suggest maybe a 15-minute time limit--is that okay, FDA? Okay.

MS. MCGARVEY: Shirley McGarvey, regulatory consultant to ATC.

With respect to the range of approval, at several earlier Panel meetings, there has been quite a bit of discussion with respect to what the range should be in the context of a protocol. Dr. Scott McRae articulated this best, I believe, back in the middle of 1995 when he talked about the difficulty, because of the low incidence of the higher levels of correction in the population, that if we

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left the patient entry criteria on the high side open-ended, we would have some data available as opposed to having no data available and restricting the indication for use.

This has also occupied quite a bit of discussion time at the Eye Care Technology Forum where we were looking at trying to come to some terms with respect to how many patients in each cell should be the basis for approval.

The recommendation at the meeting immediately prior to the Guidance Document that was discussed at the October Panel meeting suggested that we look at the full range, and where the population represents 90 percent of that correction within the population, that the labeling specifically provide the data for those areas, because you could anticipate making statistical statements for those ranges of correction; that for the higher ranges of correction, where insufficient numbers were in the higher cells, that a trend analysis would be provided in the labeling with appropriate statements of the results and warnings with respect to the inability to draw statistical conclusions based on limited information.

The only other comment that I have is that with respect to the manner in which we should measure intraocular pressure postoperatively, I think it is a universal labeling issue for all lasers. With respect to RGP lenses, I agree

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that the time frame needs to be very clearly dictated so that the refraction is stable prior to treatment. And with respect to age, we believe that we have reasonable results for patients under 21, but if 21 is the age criterion, based on several concerns on the part of the panel, then we expect that that should be a universal limitation and not unique to any one sponsor.

DR. HIGGINBOTHAM: Thank you.

Is there anyone else representing the sponsor who would like to make a comment at this time?

[No response.]

DR. HIGGINBOTHAM: Is there anyone on the panel who would like to comment on any of the four questions which we have just reviewed, based on the sponsor's comments?

Yes?

MS. MORRIS: Lynn Morris.

I just have a question whether it is the Panel's recommendation to make 21 the age, because in all of their materials--the patient information booklet and so on--it says 18. It is an official recommendation, then, by this Panel that it be 21?

DR. HIGGINBOTHAM: Based on the reviewers' comments and the discussion of the Panel, that has been the consensus. Would you like to offer another proposal?

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MS. MORRIS: No. I would certainly recommend that as well.

DR. HIGGINBOTHAM: Are there any other comments?

Dr. Bullimore?

DR. BULLIMORE: Not as much a question as a point of information. I assume that we are only here to pass opinion and vote on this particular PMA. We are not allowed to discuss any other past or future PMAs, so in that regard, I think we can't go any further than our mandate.

DR. HIGGINBOTHAM: Since you have the floor, Dr. Bullimore, do you wish to raise your other question about the postoperative use of steroids?

DR. BULLIMORE: That's really just a question for my colleagues on the panel. We have talked before about bilateral/unilateral surgery being a practice of medicine issue. I raised the issue again about using steroids to titrate the refractive error and whether that's considered a practice of medicine or optometry issue.

Any comment from anybody--a point of information only.

DR. HIGGINBOTHAM: Perhaps we can table that for another time.

Dr. Macsai?

DR. MACSAI: I'll make a comment. I think it is a

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practice of medicine issue, and I think sponsor has a protocol they have laid out and will hopefully provide in any training session to users of the device.

DR. HIGGINBOTHAM: Dr. McCulley?

DR. MACSAI: I'm not sure about the terms we are using here. I think that if a sponsor has a protocol, the use of postoperative devices, medications, needs to be standardized and not just left as a, quote, "practice of medicine issue" in the course of a study, because that gives us an independent variable.

DR. BULLIMORE: Okay. I'm satisfied.

DR. HIGGINBOTHAM: Thank you.

Dr. Rosenthal, do you have a comment?

DR. ROSENTHAL: As I understand it, the use of the steroids post whatever you are doing to the cornea is a practice of medicine issue, but I don't know if it's meant to be put in the labeling.

DR. HIGGINBOTHAM: Dr. McCulley?

DR. McCULLEY: You were talking to Dr. Chambers when I said what I said. I think that in a protocol, the use of postoperative devices and medications should be standardized and not left to independent practice of medicine variability. It introduces an independent variable on which we have no control that can influence the outcome.

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So for a protocol and for a study, then it should be standardized. What happens once it is in the marketplace then becomes a practice of medicine issue.

DR. HIGGINBOTHAM: Dr. Rosenthal?

DR. ROSENTHAL: Help, Morris.

DR. HIGGINBOTHAM: Dr. Waxler?

DR. WAXLER: Morris Waxler.

This Panel--not necessary to all the people in this particular room at the moment--but several Panel sessions ago in the run-up to the guidance, this issue was vigorously discussed, and we got input from the office director, and there were many, many discussions. And I think we concluded at that time that this is an issue of practice of medicine. I think there was rather general consensus. I hate to see it revisited again, but I don't think it's appropriate on the back of this particular applicant.

DR. BULLIMORE: Okay. I apologize, Morris.

DR. HIGGINBOTHAM: Okay. Any other comments from the Panel?

Dr. Macsai?

DR. MACSAI: I still have concerns regarding labeling for women using hormonal supplements. It does seem that the results were not equal in that population, and there should be something in the labeling to indicate that

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both to patients and doctors.

DR. HIGGINBOTHAM: Can we return to that comment once we have voted, and you can specify it at that point?

DR. MACSAI: Sure.

DR. HIGGINBOTHAM: Okay. Ms. Sally Thornton?

MS. THORNTON: I just wanted to refresh your memories about the three recommended options for voting--approval meaning there are no conditions attached.

Approvable with conditions means that you delineate the conditions prior to voting. All of the conditions will be discussed by the Panel and listed by the chair.

And with not approvable, you need to recognize that there are data that do not provide reasonable assurance that the device is safe, reasonable assurance has not been given that the device is effective or that the proposed labeling to be false and misleading. Then, following that vote, you would identify the measures you think are necessary to bring the application to approvable form--just to reiterate those things for you, Dr. Higginbotham.

DR. HIGGINBOTHAM: Thank you, Ms. Thornton.

You have heard the options. What is your pleasure? Is there a motion?

Dr. Bullimore?

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DR. BULLIMORE: I move that this PMA be approvable, within the range of up to 8 diopters of spherical equivalent, up to 4 diopters of astigmatism, over the age of 21 years--sorry--21 or over--and not encroaching within 250 microns of the corneal endothelium.

DR. HIGGINBOTHAM: Is there a second?

DR. McCULLEY: Second.

DR. HIGGINBOTHAM: Discussion?

DR. McCULLEY: Call for the question.

DR. HIGGINBOTHAM: Are those conditions for labeling, just for clarification.

DR. BULLIMORE: I think--the first three are certainly conditions of approval. The 250 micron, I'll leave that to the FDA's pleasure.

DR. HIGGINBOTHAM: Okay.

Dr. Macsai--excuse me, Dr. Macsai. Dr. Rosenthal?

DR. ROSENTHAL: If I may just make a comment, you have certainly raised an important issue and one which we have to take on board quite seriously. I don't know whether you want the Panel to make the decision or if you would like us to make the ultimate decision based on the discussion.

DR. MACSAI: About what?

DR. ROSENTHAL: About the women with--

DR. HIGGINBOTHAM: That was the comment you were

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about to make.

Dr. Macsai, did you want to restate your--

DR. ROSENTHAL: We are happy for you to request that it be included and voted on, or we would be happy for you to leave it up to us. I am happy either way.

DR. MACSAI: Well, I was going to offer a friendly amendment to our motion.

DR. ROSENTHAL: By all means, Dr. Macsai.

DR. HIGGINBOTHAM: Okay. I hear an amendment coming.

DR. MACSAI: My friendly amendment to Dr. Bullimore's motion is that in the labeling there be some discussion or presentation of data differences or outcome differences in women on hormonal replacement therapy, and that with that friendly amendment, we then vote.

DR. HIGGINBOTHAM: Is there a second to that amendment?

DR. SUGAR: Yes.

Dr. Bullimore, do you accept the amendment?

DR. BULLIMORE: I do.

DR. HIGGINBOTHAM: You sound so sweet.

Dr. Pulido, you had your hand up.

DR. PULIDO: No. I put it down.

DR. HIGGINBOTHAM: Okay. Well, that gives Dr.

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McCulley a chance.

DR. McCULLEY: Point of clarification. You said something about the 250, whether that was a condition. That is either a condition or a labeling issue. You are not withdrawing that as part of the recommendation for approvable.

DR. BULLIMORE: Well, why don't you clarify since you were the one who argued it so succinctly? Do you think it should be a condition, or do you think it should be a labeling issue?

DR. McCULLEY: That's an operational point for the FDA. I think they need to deal with it effectively, that we want approval labeling to address that it should not invade the posterior 250 microns of the corneal stroma or come within 250 microns of the endothelium, which is I think how you stated it.

How that is dealt with by the FDA, I'll leave to them.

DR. BULLIMORE: That was certainly the spirit of my motion.

DR. HIGGINBOTHAM: Thank you, Dr. Bullimore.

Dr. Rosenthal?

DR. ROSENTHAL: Dr. Chambers, from the Center for Drugs, just informed me that if we do wish to put a

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statement in the labeling regarding estrogen therapy, we will have to get it cleared through the Center for Drugs.

DR. PULIDO: I would recommend, then--

DR. HIGGINBOTHAM: Dr. Pulido, please take the floor.

DR. PULIDO: Thank you, Dr. Higginbotham.

I would recommend, then, amending Dr. Macsai's amendment, or taking it off the floor, back to allowing the FDA to consider her concerns.

DR. HIGGINBOTHAM: I take that as a motion?

DR. PULIDO: Yes.

DR. HIGGINBOTHAM: Is there a second?

DR. JURKUS: Second.

DR. HIGGINBOTHAM: Dr. Bullimore, do you accept that amendment?

DR. BULLIMORE: I do.

DR. HIGGINBOTHAM: Okay.

Any other comments?

DR. PULIDO: Call for the question.

DR. SUGAR: Wait, wait. I'd like an explanation. We haven't voted on the amended amendment.

Jose, could you say why you are withdrawing it--because you are afraid of having--

DR. HIGGINBOTHAM: Dr. Pulido? Thank you, Dr.

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Sugar.

DR. PULIDO: No. I would just like to see a longer evaluation of this problem. I'd like the industry people to get involved with the FDA to look at this more carefully before we consider it for labeling purposes.

DR. HIGGINBOTHAM: Okay. Are there any other comments from the FDA? Does the FDA wish to make any additional comments at this point?

DR. ROSENTHAL: No, we do not.

DR. HIGGINBOTHAM: Okay. Let me just state what we are voting on at this point, if I may. We are voting on an approvable PMA with conditions, and those conditions are as follows. Patients with errors up to minus 8 diopters spherical equivalent to be further clarified by the FDA, up to 4 diopters of astigmatism, preservation of the posterior 250 microns of the corneal stroma, and 21 years of age and over.

Does everyone agree with that as stated? We don't have an amendment anymore.

Okay.

DR. McCULLEY: Call for the question.

DR. HIGGINBOTHAM: All those in favor, please indicate by raising your hands.

[A show of hands.]

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DR. HIGGINBOTHAM: It is unanimous. Thank you.

Any other comments or questions?

Yes?

DR. MACSAI: I chastised the sponsors for comparing their data with that of other applicants, and now I am about to do this same thing. This issue of women and hormones can't be ignored and swept under the table. It was brought up at a previous review of an approved device and swept under the table then, and now it is swept under the table again, and we owe it to the public, and we owe it to those women to figure it out.

DR. HIGGINBOTHAM: Okay.

Before we proceed, if you will allow me, Dr. Pulido, I'd like to poll the voters, and please state why you voted the way you did.

Dr. Bullimore?

DR. BULLIMORE: This is an excellently well-prepared PMA. The data were very complete, the accountability impressive. I voted for the motion.

DR. HIGGINBOTHAM: Dr. Sugar?

DR. SUGAR: I voted for the motion for the same reason--that the presentation was very complete and compelling.

DR. HIGGINBOTHAM: Dr. Macsai?

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DR. MACSAI: I voted for approval because the device does appear to be safe and effective in the stated ranges. However, I still feel strongly that if the sponsors found problems in one sub-population, that being women on hormone therapy, that should be further investigated and considered strongly as a labeling issue.

DR. HIGGINBOTHAM: Thank you.

Dr. Pulido?

DR. PULIDO: I voted for approval because it was a well-designed study. I did have concerns about the higher levels of myopia and astigmatism, and that has been taken care of.

We have already mentioned that this hormonal problem needs to be looked at more carefully, and I'm sure the FDA is going to take that into guidance.

DR. HIGGINBOTHAM: Dr. McCulley?

DR. McCULLEY: I agree with what Dr. Pulido said.

DR. HIGGINBOTHAM: Dr. Jurkus?

DR. JURKUS: I agree with what Dr. McCulley said.

DR. HIGGINBOTHAM: Thank you.

Dr. Pulido, any other comments?

DR. PULIDO: No.

DR. HIGGINBOTHAM: Does anyone want to make any other comments?

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DR. McCULLEY: Move for adjournment.

DR. HIGGINBOTHAM: Thank you, Dr. McCulley. Is there a second?

DR. PULIDO: Second.

DR. HIGGINBOTHAM: Thank you. Have a happy Valentine's Day. The meeting is adjourned.

[Whereupon, at 4:25 p.m., the proceedings were concluded]