UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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OPHTHALMIC DEVICES PANEL

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March 27, 2009
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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ALICE Y. MATOBA, M.D.	Voting Member
KAREN BANDEEN-ROCHE, Ph.D.	Temporary Voting Member
JANET S. SUNNESS, M.D.	Temporary Voting Member
JANET SZLYK, Ph.D.	Temporary Voting Member
DAVID C. MUSCH, Ph.D.	Temporary Voting Member
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MRS. JANET GRANT
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MR. DAN ROBERTS

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M E E T I N G

(8:00 a.m.)

DR. WEISS: Okay. If everyone will take their seats, I would like to call this meeting of the Ophthalmic Devices Panel to order.

I'm Dr. Jayne Weiss. I'm a Professor of Ophthalmology, Director of Refractive Surgery at Kresge Eye Institute, Wayne State University School of Medicine in Detroit, Michigan. I'm Chairperson of this Panel today, and I'd like to say good morning. Welcome to Gaithersburg to everyone.

At this meeting the Panel will be making recommendations to the Food and Drug Administration on the Premarket Approval Application, PMA P0500034, for the VisionCare Technologies, Incorporated, IMT, Implantable Miniature Telescope.

Before we begin, I'd like to ask our Panel members and the other FDA staff seated at this table to introduce themselves, and if you could please state your name, your area of expertise, and your affiliation and position. Dr. Eydelman.

DR. EYDELMAN: Malvina Eydelman, Director, Division of Ophthalmic and ENT Devices.

DR. MUSCH: David Musch. I'm a Professor at the University of Michigan. My expertise is in

epidemiology.

DR. EDRINGTON: Tim Edrington, Cornea and Contact Lens Service, Southern California College of Optometry.

DR. SUNNESS: Janet Sunness. I'm Medical Director of The Hoover Services for Low Vision and Blindness, and my expertise is in medical retina, macular degeneration, and low vision.

MS. FALLS: Deborah Falls, FDA, Executive Secretary in training.

MR. SWINK: James Swink, Acting Executive Secretary.

DR. WEISS: And Jayne Weiss. I've already introduced myself. I'm a cornea specialist and an anterior segment surgeon, refractive surgeon.

DR. BANDEEN-ROCHE: Karen Bandeen-Roche, Professor at Johns Hopkins. My expertise is in biostatistics.

DR. MATOBA: Alice Matoba, Associate Professor at Baylor College of Medicine, and my field is cornea and external diseases.

DR. SZLYK: Janet Szlyk. I'm the Executive Director of The Chicago Lighthouse for people who are blind or visually impaired, Adjunct Professor of Ophthalmology and Visual Sciences, University of

Illinois at Chicago. My field of expertise is low vision rehabilitation.

DR. FERRIS: Rick Ferris, Director of the Division of Epidemiology and Clinical Applications at the National Eye Institute, and my ophthalmology subspecialty is medical retina.

MR. BUNNER: I'm Richard Bunner. I'm the consumer representative. I'm a past board member of Prevent Blindness America, past Government Affairs Chair, and retired public health administrator.

MS. NIKSCH: I'm Barbara Niksch. I'm Vice President of Regulatory Quality and Clinical at Visiogen. I'm serving as the industry representative.

DR. WEISS: Thank you. If you haven't already done so, please sign the attendance sheets that are on the table by the doors outside, and if you wish to address this Panel during one of the open sessions, please provide your name to Ms. AnnMarie Williams at the registration table.

If you are presenting in any of the open public sessions today and have not previously provided an electronic copy of your presentation to FDA, please arrange to do so with Ms. Williams.

And I also will note for the record that

the Voting Members constitute a quorum as required by 21 C.F.R. Part 14. I'd also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

Mr. Swink, the Acting Executive Secretary for the Ophthalmic Devices Panel, will now make some introductory remarks.

MR. SWINK: I will now read the Conflict of Interest Statement.

The Food and Drug Administration is convening today's meeting of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the Panel are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and consultants of this Panel are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussions of today's meeting, members and consultants of this Panel who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of the 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert testimony, contracts/grants/ CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

Today's agenda involves a discussion on a Premarket Approval Application for the IMT, Implantable Miniature Telescope, sponsored by VisionCare Technologies, Incorporated. The IMT is a visual prosthetic device which, when combined with optics of the cornea, constitutes a telephoto lens. This is a particular matters meeting involving a specific party.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) and Section 712 of the FD&C Act to Drs. Karen Bandeen-Roche and David Musch. Dr. Bandeen-Roche's waiver addresses an imputed interest with a PMA sponsor from whom her institution received less than $100,000, but she was not compensated. Dr. Musch's waiver addressed an imputed interest with a PMA sponsor from whom his institution received between $100,000 and $150,000, but he was not compensated. These waivers allow the individuals to participate fully in today's deliberations.

FDA's reason for issuing the waivers are described in the waiver documents which are posted on FDA's website at www.fda.gov. Copies of the waivers

may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Barbara Niksch is serving as the industry representative, acting on behalf of all related industry, and is employed by Visiogen, Incorporated.

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

FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue. Thank you.

I will now read the appointment to temporary voting status. Pursuant to authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27, 1990, and as amended on August 18, 2006, I appoint the following individuals

as voting members of the Ophthalmic Devices Panel for the duration of this meeting on March 27, 2009: Dr. Karen Bandeen-Roche, Dr. Janet Sunness, Dr. Janet Szlyk, Dr. David Musch, Dr. Eve Higginbotham, Dr. Frederick Ferris.

In addition, I appoint Jayne S. Weiss, M.D., to act as Temporary Chair for the duration of this meeting.

For the record, these individuals are special government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This was signed by Daniel G. Schultz, M.D., Director, Center for Devices and Radiological Health and dated March 26, 2009.

Before I turn the meeting back over to Dr. Weiss, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting, Inc.

Information on purchasing videos of today's meeting can be found on the table outside of the meeting room.

Presenters to the Panel who have not

already done so should provide FDA with a hard copy of their remarks, including overheads.

I would like to remind everyone that members of the public and the press are not permitted around the Panel area beyond the speaker's podium.

The press contact for today's meeting is Peper Long, and I request that reporters wait to speak to FDA officials until after the Panel meeting.

Finally, as a courtesy to those around you, please silence all your electronic devices if you have not already done so.

DR. WEISS: Thank you. I'd also like Dr. Higginbotham to introduce herself as far as her position, her expertise, and her affiliation.

DR. HIGGINBOTHAM: Thank you. I am Dr. Eve Higginbotham. I'm Dean and Senior Vice President for Academic Affairs at Morehouse School of Medicine. I'm also a Professor of Ophthalmology and Visual Sciences at Emory School of Medicine. I have been a glaucoma specialist for more than 25 years, and I'm happy to be here.

DR. WEISS: I notice you started hesitating when putting in the number of years there, Eve.

DR. HIGGINBOTHAM: Yes.

DR. WEISS: We will begin with the updates

now from FDA. The first presenter is Dr. Malvina Eydelman, Director of Division of Ophthalmic, Ear, Nose and Throat Devices.

DR. EYDELMAN: Good morning. I just wanted to welcome everybody, and I wanted to thank my staff who has done an incredible amount of work in preparation for today, and the Panel members who I know had a lot of reading to do in preparation for today. So we look forward to a very productive day.

With that, I want to turn it over to Dr. Kesia Alexander, who is going to give you branch updates.

DR. ALEXANDER: Thank you. Good morning. My name is Kesia Alexander, and I'm the Branch Chief of the Intraocular and Corneal Implants Branch, ICIB, and I will be providing updates for ICIB and the Vitreoretinal and Extraocular Devices Branch, VEDB.

Since our last meeting in June of 2008, we approved four intraocular lenses in ICIB and one extended wear contact lens in VEDB. The approvals are as follows:

P060022, Bausch and Lomb's Akreos Posterior Intraocular Lens, was approved on September 5, 2008.

P080004, Hoya Surgical's iSpheric Intraocular Lens, was approved on September 26, 2008.

P080010, Abbott Medical Optics' TECNIS Multifocal Foldable Posterior Intraocular Lens, was approved on January 16, 2009.

P080021, Advanced Vision Science's XACT Foldable Acrylic Intraocular Lens, was approved on February 2, 2009.

P080011, CooperVision's Biofinity, Comfilcon A, Soft Extended Wear Contact Lens, was approved on November 19 of 2008.

At the last Ophthalmic Devices Panel meeting on June 10th, we convened a Panel of outside experts to consider ways to improve contact lens safety. We sought Panel input on modifications to the existing guidance document for multipurpose contact lens care products.

In response to the advisories from the Panel meeting, we have been working on several improvements in our communications with the public regarding contact lens related safety issues. Consequently, we have updated our contact lens website to include an information box on the home page reflecting recommendations of the Panel such as using rub and rinse for disinfecting the lens rather than using no-rub technique, not topping off solution in the lens case, and not exposing the lens to water.

In addition, we have added a contact lens solutions and care products page to the website and a link to MedWatch with the red phone reporting button for reporting eye problems possibly associated with the lens and lens care product use.

We also convened a contact care product workshop titled, Microbiological Testing of Contact Lens Care Products, on June 22 and 23 of 2008, in collaboration with the American Academy of Ophthalmology, American Academy of Optometry, American Optometric Association, and the Contact Lens Association of Ophthalmologists. The workshop was held at our White Oak Facility.

The goals of the workshop was to gain consensus on the critical test method parameters for evaluating the activity of contact lens care products against *Acanthamoeba* and to discuss the critical elements for new or modified disinfection efficacy test methods that simulate real world consumer use conditions. While consensus was not obtained on all topics, great strides were made in tackling an elusive foe.

These are just a few ways FDA's working to ensure that patients and physicians have current, accurate information to help them with their

decisions about contact lenses and contact lens care products.

As we move forward with our plan implementing the suggestions and advisories for improving test methodologies, for evaluating contact lens care solutions, we also explore additional ways that we can improve the quality of information available to the public. Thank you.

DR. EYDELMAN: Now I would like Mr. Kwame Ulmer to give an update.

MR. ULMER: Good morning. I'm Kwame Ulmer, Chief of the Diagnostic and Surgical Devices Branch, and this morning I'll be giving an update on activities in our branch.

On April 5, 2008, FDA convened a Public Advisory Panel of outside experts to listen to patient experiences with LASIK and consider how to improve information for patients and physicians about LASIK.

In response to the feedback, from public and LASIK experts, we've been working on several improvements in our communications with the public regarding LASIK-related safety issues. Our accomplishments to date include FDA LASIK website. We've made it easier for LASIK patients to report

problems within two clicks from the FDA LASIK website. On the FDA LASIK home page, select report a problem at the bottom left column, and then select report a LASIK problem to MedWatch.

We've updated the other resources section of the website to provide a wider range of information about LASIK to patients and physicians.

We've clarified the contact us section on how to submit a question about LASIK to FDA and how to submit a comment or concern about LASIK to the public record.

SightNet, we've updated related information in SightNet, a program used by healthcare professionals at participating facilities to share concerns about potential safety issues with ophthalmic medical devices and report problems to FDA. The updated information includes an emphasis that halos, glare, night vision problems, and dry eye from LASIK should be reported to FDA.

Patient information card, we've worked with the American Academy of Ophthalmology to develop a card that physicians can fill out with the patient's eye measurements before LASIK surgery. Patients can keep this card to help the doctor calculate the lens implant power should they need to have future

cataract surgery.

FDA recognition of ANSI laser systems for corneal reshaping. In March of 2009, FDA officially recognized the new LASIK standard from the American National Standards Institute, ANSI, entitled Laser Systems for Corneal Reshaping. FDA, as a member of ANSI, works closely with this and other national and international standards organizations. This group meets to develop and come to a consensus on appropriate national and international standards for device testing and performance.

LASIK docket. We've opened a public docket for LASIK so that any interested person can post questions, comments, or concerns regarding LASIK. This docket is web-based, and all comments submitted are able to be viewed by the public. All comments on the document are examined in excess by FDA staff on a regular basis. The LASIK docket can be found at www.regulations.gov and can be accessed with the keyword, LASIK, or typing in the LASIK docket number FDA-2008-N-0488.

These are just a few of the ways FDA is working to ensure that patients and physicians have current, accurate information to help them with their decisions about LASIK and to facilitate their

reporting problems. As we continue to monitor the safety and effectiveness of LASIK, we'll also explore additional ways that we can improve the quality of information available to the public about LASIK and ways to ensure that FDA receives better information about problems with LASIK. Thank you.

DR. EYDELMAN: That's completes the vision updates.

DR. WEISS: Thank you very much.

DR. EYDELMAN: We will now have Dr. Danica Marinac-Dabic give postapproval study program update.

DR. MARINAC-DABIC: Good morning, ladies and gentleman. Dr. Weiss, Dr. Eydelman, distinguished members of the Panel.

My name is Danica Marinac-Dabic. I'm the Director of the Division of Epidemiology at the Office of Surveillance and Biometrics. My group is in charge of the design, review, and oversight of FDA mandated postapproval studies, and also we are in charge of the CDRH-funded epidemiologic research program. Both of those programs are designed to address specific postmarket questions that still remain unanswered at the time of the device approval. So it is my pleasure today to give you an update on the recent changes that have occurred at CDRH on the

ways how we handle the postapproval studies.

As you can see from this slide, postapproval studies are only one tool that CDRH utilizes when addressing the important postmarket questions. As you can see, we have a number of passive and enhanced type of surveillance that are in place. We also have the postmarket surveillance program under Section 522 of the Act, and as I said, we have also established the CDRH epidemiologic research program which is growing, and we have currently 23 ongoing epidemiologic research studies.

At the time of the device approval, the reasonable assurance of safety and effectiveness of medical device is established, and the specific PMA receives the approval. So why do we need postapproval studies?

Postapproval studies can help us gather essential postmarket information about longer-term performance of medical devices, including the effects of retreatments and product changes that are very frequent as we all know.

Also after the product is approved, then the device is being used in a much wider population of physicians and much wider population of patients and what we call the real world type of setting. And

postapproval studies can be very useful to give us information about how a medical device performs in those types of situation.

Postapproval studies can be also very useful to study the effectiveness of training programs. As you know, many devices require rigorous training. There's sometimes very steep learning curves. Postapproval studies can be a useful tool to design the study around these important endpoints that we are interested in, in postmarket setting.

We can also study the performance of subgroups that were not properly represented in the premarket setting. So those subgroups were not represented in the premarket clinical trials, postapproval studies might be an avenue to address that performance.

If we have any outcomes of concerns that still remain, postmarket, whether those are safety or effectiveness concerns, we can design a postapproval study to answer those questions.

This is certainly a way to balance premarket burdens as we would like to help our colleagues from industry to bring the devices quickly to the market but also to help address some important questions in the postmarket setting.

And, finally, we also recommend Panel recommendations. We very much value your recommendations based on your clinical expertise to help us design better postapproval studies in the postmarket setting.

This is the legal authority again that we have, to continue asking for the safety, effectiveness, and reliability data in the postapproval setting, and again those can be safety or effectiveness; if the remaining questions are not essential for the establishment of the assurance of safety and effectiveness at the time of the approval, but important postmarket questions, we can ask for postapproval studies.

It is important to say that postapproval studies should not be used to evaluate unresolved issues from the postmarket phase that are essential for the initial determination of the device safety and effectiveness.

During the last four years, the CDRH had committed significant amount of resources to transform the postapproval studies program, and these are our main goals. We wanted to enhance the scientific rigor of postapproval studies. We would like studies to have clear objectives. We would like

the objectives to have hypotheses, to have comparison groups, studies, that once upon completion, can be properly interpreted and help us come up with the findings that then can be incorporated into labeling and provide labeling changes, if necessary, based on the findings.

We also, by this transformation, wanted to establish and maintain accountability for the postapproval studies commitments, both on the industry side and the FDA side. So we have made a commitment that we will review all the submissions within 60 days and provide a response to industry. We also are expecting our colleagues from industry to provide timely responses to us, and we have established the tracking system to properly track those responses.

Again, one of the other major goals of the transformation was to enhance the cooperation between our premarket and postmarket functions. So whatever knowledge is gained in the postmarket setting, we would like to share with our premarket colleagues.

And finally, we are very much committed to increase the transparency with the public, and this presentation is one of the examples of our strategies to inform the public about these changes in a timely

fashion.

Again, this transformation was very comprehensive, arranged from the changes in oversight and tracking, major changes in how the PMA review is being conducted, and also we put together the guidance document and also have our web postings of the status of current ongoing postapproval studies. We instituted these routine updates to the postmarket advisory panels, and we are also establishing stronger, informal relationships with other public health partners.

As I said, the oversight had been transferred in 2005 from Office of Devices and Evaluation to Office of Surveillance and Biometrics, and these are some of the major changes that have happened since that time.

I would say from the epidemiologic prospective and from the postmarket section, this was crucial for us to be included in every PMA review team. In 2005, we started being part of every postmarket application review team. The epidemiologist's role would be to review the postmarket application submission with an eye toward what might be those postmarket questions that still need answering in the postmarket setting. You know,

the decision about need for a postapproval study certainly will be made by the team itself, and not only by the epidemiologists on the team, but once the decision is made, we're working directly with industry to help them design this study, and our goal is at the time of the device approval, we will have the protocol ready to go.

And I always like to cite one example that we have from the cardiovascular community that we were able to enroll the first patient into postapproval study 48 hours after the device approval was issued. That means that we worked with industry to develop the protocol. We also have obtained the IRB approval, and the study was ready to go at the time of the approval.

Once the decision is made to approve the product, then the Office of Surveillance and Biometrics takes the lead, and we are the ones who review the reports. We make sure that those reports come on time, and we look into the results, communicate with industry, and help them if there are any obstacles to implement those postapproval studies.

This is the link to our guidance document. We certainly acknowledge that our goal is, in

addition to having the scientifically rigorous studies, those studies should be least burdensome, and we find out that really we would like to propose that the way to least burdensome is to discuss postmarket balance as early as possible which we are doing during the premarket phase.

As I said, in terms of the accountability, we instituted postapproval studies tracking system, and we now track all postapproval studies. Just to give you a sense how many of those studies we currently have, we have 166 ongoing postapproval studies for all devices; 89 of those had been instituted after 2005, after the transformation had occurred and we took over the program, and those are posted on our webpage.

These are the study definitions. I'm not going to go into those details, but those are the definitions for the status that we use and translate them into status that goes on the web.

This is the link to the webpage. It went live 2007. Again, it is being updated monthly, and this is how it looks. You can go and search, and it's certainly a link to the PMA database. You can see what information is in there. We do not share the information that's specific to the company but,

you know, you will see the status both for the progress of the study and the status of the report in there.

It is very important that we communicate to our Panel members, and we would like to share with you the strategy that we started, and we would like to continue with that. At every Panel, we will give you an update on the major developments in the postapproval studies program, and in those instances where there is specific issue that we would like to discuss with the Panel, we will call for a specific postmarket update to the Panel.

At that time, we would invite our industry also to give a presentation, and we would jointly present to the Panel and perhaps come with some questions for which you may give us our input, but this is just general today. It's just a general presentation.

The success of our postapproval studies program is very much dependent on the engagement of our public health partners, and to that effect, we establish this robust CDRH epidemiologic research program. We have developed numerous contracts, grants, IAGs with different organizations, including our sister organizations within DHHS, including NIH

and ARC, also contracts with professional organizations and academia, and again with a goal to answer important postmarket questions for the performance of medical devices.

In addition, I would like to let you know that on June 4th and 5th of this year, we are sponsoring, along with Food and Drug Law Institute, an implementation workshop for postapproval studies, again to discuss what are the obstacles that sponsors may have in conducting the postapproval studies and help them move those studies forward.

Another workshop on postapproval studies is being scheduled on September 14th and 15th, again in cooperation with Food and Drug Law Institute and Agency for Healthcare Research and Quality. At that time, we will target the methodology and how we can design better postapproval studies and using innovative methodologic approaches.

And just very quickly, to give you snapshot of the -- original PMAs and Panel track supplements approved from 2005 to 2009, and the number of the postapproval studies initiated after that. These are four observational studies, just very briefly. I'm not going to discuss them in detail.

As you can see as far as the reporting

status, we have one study that we received the report on time. Two reports are still pending. One report is overdue. Again, we are in constant communication with our colleagues from industry and helping them address discretions and helping them meet their study timelines.

This is the study progress of those studies. Again this is just a snapshot of the post-2005 initiated postapproval studies in ophthalmic devices.

And finally, I would like to conclude that our vision is to have these studies to answer only important postmarket questions. We would like studies to be founded on good science, to be realistic, that can be conducted in a timely manner, give us accurate findings, and certainly we would like to keep all our stakeholders apprised throughout the process. Collaboration, I cannot stress enough how important it is for us to continue with collaboration within the CDRH, with Dr. Eydelman's group, on both research projects and postapproval studies program. And if we practically address many of these issues, we foresee that we will have less enforcement options that need to be done in the future.

We understand these are higher expectations, and with higher expectations usually come concerns. We would like to put those concerns into proper context of asking the right postmarket questions at the right time. So again, it's more work for us. It is more work for our regulated industry, but we believe that by completing these studies in a timely fashion, we help not only our own agency to make proper decisions but we will inform the public in a timely fashion on how those medical devices perform when they are approved and being used in the real world setting. Thank you very much.

DR. WEISS: Thank you. We now have concluded the FDA updates, and we'll proceed to the first open public hearing portion of the meeting.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of any individual's presentation. For this reason, FDA encourages you, the open public hearing participant or the industry speaker, at the beginning of your written or oral statement, to advise the Committee of

any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, the financial information may include the sponsor's direct payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

We have presently four individuals who have asked to speak this morning. Mrs. Marian Orr is the first speaker, and if you, Mrs. Orr, could come up to the podium. Each of the public speakers will have five minutes to speak to the Panel. There will be a yellow light that will light when you have one minute left, and the red light will go off at five minutes. So thank you. Mrs. Orr.

MS. ORR: I knew I had a choice. Once I was diagnosed with macular degeneration, I knew I had a choice of how I was going to live my life. My father and his brother were both blind, and I saw the life they lived. They were blind for most of their

later years, and I witnessed all the things that they missed.

Once I was approached about the telescope, I knew that it was my only choice if I did not want to miss most of my later years. After the telescope was placed, I continued to work a full-time job, enjoy leisure activities and see my children and grandchildren through milestones in their lives.

When I was diagnosed with macular degeneration, I was working as a legal secretary and an accountant for a law firm. I was sent to the Low Vision Clinic where I was then approached about the telescope. After the telescope was placed, the Low Vision Clinic suggested tools for vision, such as a large screen computer monitor, software for the computer that enlarged everything, and a CCTV which enlarged font on papers that were placed under it. This device has allowed me to continue working for two more years before I retired completely.

I continue to leisurely read, which is one of my favorite past times. I purchased glasses with a large magnifying glass in my good eye which enables me to read large print as well as regular print.

I am now connected with the North Carolina Association of the Blind, and they mail me books in

large print, and I mail them back with no postage required. I am able to read the newspaper, large print books as well as the regular print books, including the hymnals at my church where I continue to be very active.

I plan activities monthly for our senior citizens group to attend, and I'm able to plan these activities on the phone with the help of the telephone company. I receive 411 service free for local telephone numbers.

I volunteer once a week as a lunch buddy at a nearby elementary school. I visit with a less fortunate child who is in the second grade. I've been volunteering for five years, and they're a joy to work with. I enjoy being a part of their school year, watching them grow and develop as students.

To this day, I continue to live alone. The only thing I can't do is drive, but seeing the price of gas, that's not a real hardship. I have very loyal friends and family who are able to help me get to appointments, church, and shopping. I have lunch with friends at least twice a week. I am still able to watch movies and television without any problems.

As you can tell, I've had a very active life prior to my diagnosis as well as after my

diagnosis. It has been a blessing to me to be able to have an active life with the vision that enables me to do the things that I like to do. I could not have had this active life without the telescope to bring my eyesight to where it is now.

Before the transplant, I could not see your face, just around your face, but now I am able to see your face directly. I did lose the peripheral vision in the implanted eye, but I can always turn my head to correct that.

When I was approached about speaking to the FDA Panel, I knew it was something that I had to do. I have lived a life fulfilled, and I know many friends who have been diagnosed with macular degeneration that would benefit from the telescope.

VisionCare provided me the funds to make this trip so I could speak on behalf of the telescope.

DR. WEISS: Thank you very much. Keep up the good work. Mr. Billy Fulmer or Fulmer will be our next speaker.

MR. FULMER: Good morning. My name is Bill Fulmer, and I'm from a little town, Leeds, Alabama, and 12 years ago, I found out I had macular degeneration, and I went to the doctor and he didn't

make me feel too good. And I got to where as time passed on, I couldn't read the eye chart. I would go into the supermarket, couldn't find my wife, go outside at the curb. I would fall, and all at once, I saw ABC World News Tonight with Peter Jennings where this company had a telescopic lens for macular degeneration.

I immediately called my son, and he got me lined up at Emory University, and Atlanta called me for an appointment. They explained it to me. I went home with two lens, with a little plastic thing, to decide what lens I wanted. She said take about two weeks. Well, two days I found out which one I wanted, and I went back to Atlanta, told her which one. Then I went through some tests for two or three more trips, and the doctor told me that he was ready to implant it in my eye.

We went up to Atlanta at 7:00 that morning. He started, put it in my eye. He gave my wife a prescription for pain and said my eye would be real black. We went to the motel. He wanted to see me the next morning. We went to the motel and I didn't take a pain pill. I felt all right. We got up the next morning and went to the hospital. He took the patch off and immediately I saw the eye chart, and I

said, oh, yeah. And so he said, go home, come back in about, I don't know, a month or so.

So I went home, and going home and when we hit the freeway, I told my wife, on the left-hand side traffic coming, I said I can see that big trailer truck. There's a red car coming by. So she said, yeah, and as we got down the highway, I said I see a bridge way down there, and I said I think it's an exit. When we got close to it, we passed a little sign and I said that's a sign, 70 miles an hour. She said, yeah.

When we got to the sign, I didn't know what town it was because I was looking at the small print and I saw exit. So we got home and ever since we got home, I go to the supermarket, I can find my wife. I haven't fell, and about three years ago, a friend of mine that's with me said I'm going to Italy for a month, you want to go? I said, no, I said I don't want to go for a month. I said I want to go for two weeks. He said, no, you've got to go for a month. I've got to go for a month. I said I'll come back. My wife said, oh, no. I said, oh, yeah, I can come back.

I went to Italy. I came back. I might of not come back as good as you'd come back, but I asked

a few questions but I came back.

I got back. When I cut my grass now, I don't miss any spots. I found my wife, and the main thing is I'm 83 years old, and I'm very active, and my son ordered me some plastic molds to make some cement items for the yard. I made those cement items and gave them to people all over, and then my grandson gave me a big turtle mold this year for Christmas, and I live on a circle, and about 10 houses on that circle now has a cement turtle somewhere. I have three at my house waiting to be given to somebody else.

DR. WEISS: Mr. Fulmer, we're going to need to wrap up in a few seconds. I wish you had brought one of those so we could see it outside, however. Do you have a concluding statement to the Panel?

MR. FULMER: I'm going to end right now, and I'm going to say this much. This is the best thing that ever happened to me, and like I say, I'm 83 years old. I walked up here without a walking cane or a walker, and the reason for that is, is this, because if you sit at home in a recliner as old as I am, you're going to get stiff and you're going to get a walker or a walking cane. So I'm very happy, and I know there's a lot of people out there

that needs what I got, and I hope that I have enlightened you to pass it. Thank you very much.

DR. WEISS: Thank you very much. Thank you very much, Mr. Fulmer.

Our next speaker will be Mrs. Joann Preece.

MS. PREECE: I just want to reiterate probably all these things that those other two people have said. I'm 82. I live alone. I live in a barn. It's not as rustic as it sounds. I have a lovely apartment on the third floor of a barn, and I do my own cooking. I do my own laundry. I have a bank of windows in the front of apartment that I can see clear down the driveway, see who's showing up. I'm still very active.

But the implant has made such a difference in my life. I know that if I didn't have that, I would probably be sitting at home in a chair someplace or not living alone actually is what it would be.

So everybody has made such good points that I, you know, I want to say, yes, it's all true. And I've only stepped on my cat once in six years.

I want to acknowledge VisionCare who made it easy for me to get here. I thank you very much. Any questions?

(No response.)

DR. WEISS: Thank you very much. And the last speaker we have for the public session is Dr. Glenn Stoller.

DR. STOLLER: Dear Panel Members, good morning. My name is Glenn Stoller. I'm a practicing retina specialist in New York. It is a privilege to speak before this distinguished group, and I appreciate your willingness to hear comments from the public.

During my almost 12 years of clinical practice, I've had the opportunity to care for a very large number of patients with age-related macular degeneration. I know the spectrum of this disease very well and the range of impact it has on my patients. I stand here today as an advocate for my patients with bilateral late stage, advanced AMD who either never were or are no longer candidates for all currently available drug treatment options.

I'm proud to say I was an investigator for all of these various modalities of therapy during their clinical trials. So my desire to help patients with AMD is longstanding and heartfelt. My search for the advancements and care and management of AMD has led me to closely follow the development and

testing of the IMT, which I first learned about during a scientific presentation on the early results coming out of the FDA clinical trial for the device.

Since then I've kept up with the results through peer review literature, more specifically the one year results published in 2006 in the Journal of Ophthalmology, the 2007 article in the Archives of Ophthalmology, and the 2008 American Journal of Ophthalmology describing the two year visual acuity and safety results.

The patient population we are discussing today were well sighted for the majority of their life and then lived through the devastation of slowly or sometimes rapidly losing the central vision in both eyes. Given the prevalence of AMD, it unfortunately may be the destiny of some of the people in this very room.

At the present time, what this treatment of these patients consist of, the truth is, it is quite limited, but as an ophthalmologist, I realize it is not only my duty to care for their eyes but to also try and help them cope with their disease. I try to offer them rays of hope by talking about a growing understanding of the cause of their disease and letting them know about the potential methods that

may one day help some of them improve the quality of their life, medical technology such as the use of stem cells, retinal transplants, and prosthetic retinal chips and, of course, the Implantable Miniature Telescope. They then naturally ask me when these treatments may become available. With regard to stem cells, transplants, or prosthetic retinas, I sadly have to admit to them that these are still many years away. Almost all of them give me the same response, and I quote, "I will be dead by then." I have no comforting reply because I know in my heart for most, if not all of them, this is true. However, with regard to the Implantable Miniature Telescope, I hope this will not be the case.

Of course, I refer them for a low vision evaluation, a potentially valuable service, but my experience is that if a patient can be fitted with a low vision appliance after some period of time, it ends up sitting in a drawer. They find the unnatural act of having to move their heads back and forth to read intolerable secondary to the nausea it creates, a phenomenon which is a result of conflict between the vestibular and ocular systems. Moreover, the very limited field of view provided by these devices proves to be just too frustrating and difficult to

work with for most.

For patients who are phakic in at least one eye, they inevitably ask me whether cataract surgery will help them. In my experience, cataract surgery for almost all of these patients provides no meaningful benefit because quite simply opacification of their native lens is not what is causing the visual loss. Rather, it is the atrophic fibrous retinal scar.

I'd like to share a recent story about one such patient. One eye had already undergone cataract removal years earlier when it was still a good seeing eye. The other eye had a modest cataract. Over two years ago I told her about the IMT and that I thought it had the potential to help her achieve better vision. I would see her periodically in follow ups, about every six to eight months, and she and her family would always ask about the IMT. I would tell them it was not yet available. After years of waiting with no time arising to find out if the device would be made available, she decided to proceed with cataract surgery out of a sense of desperation.

So what became of her? She states that since her cataract surgery, things may be a little

bit brighter, but her vision is no better, and she's not the slightest bit more functional than she was before the cataract was removed. Given her lack of options, I understand her decision, but it saddens me she will no longer be a potential candidate for the IMT should it be approved.

I have many more patients just like her who still have a cataract and are holding off on cataract surgery in the hope the IMT will become available.

As an ophthalmologist, it strikes me as odd and somewhat paradoxical that we live in a society where patients with perfectly healthy eyes apart from the need for glasses are given the opportunity to have surgery for their eyes, specifically LASIK, which can result in serious permanent damage to the cornea just for the convenience of diminishing their need for glasses, if those patients who have been blinded in both eyes by age-related macular degeneration have thus far not been given access to a technology that has the potential to improve a much more fundamental need, their ability to function and cope with daily living.

Recently the FDA approved the drug Avastin for use in breast cancer, not because it extended life, rather because it extended disease free

survival, thus acknowledging that an improvement in the quality of one's life, even if it is fleeting, is worthy.

Today you have the power to improve the quality of life in those patients most severely affected by AMD, patients for which current methods of treatment are inadequate and which no other alternative methods for improving their visual acuity will become available for the foreseeable future. As a retinal surgeon, I am acutely aware that no surgery comes without --

DR. WEISS: Would I be able to ask you to start wrapping up. We're past the limit already.

DR. STOLLER: I am. I understand that no surgery comes without risk, and those risks have to be weighed against the potential benefits. I believe that the data supports that for this patient population, the potential impact and benefit of the IMT for improving visual acuity and quality of life outweighs the risks for many potential patients.

It is with the utmost respect that I ask the Panel today to make the IMT available, thus enabling us as physicians to have a full informed consent dialogue with our patients and ultimately allowing patients to choose what risks they are

willing to take for the potential benefits this device offers.

I have not received funds from VisionCare for my travel, and I have no financial relationship with the company whatsoever. Thank you for your time and consideration of my comments.

DR. WEISS: Thank you. Does anyone else from the public wish to address the Panel at this point? If so, please come forward to the podium and state your name, affiliation, and your financial interest, if any, in the device being discussed today.

(No response.)

DR. WEISS: Seeing no other members come forward, I will let you know that there will be a second open public session of the afternoon. I'd like to thank those who participated, especially the octogenarians who give me hope for the future if I ever make it that far.

And we're going to now start with the sponsor presentation for the IMT, Implantable Miniature Telescope. I'd like to remind the public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the

Panel.

We will begin with the sponsor presentation, and this will be for up to 90 minutes.

MR. HILL: Thank you. Distinguished members of the Panel, members of the FDA, good morning.

My name is Allen Hill. I'm Chief Executive Officer of VisionCare Ophthalmic Technologies.

VisionCare is the sponsor of this PMA for the Implantable Miniature Telescope or IMT. This device was invented by two individuals, Yossi Gross and Isaac Lipshitz. This PMA covers the use of the implantable telescope for improving vision in patients with moderate to profound vision impairment due to bilateral, end stage age-related macular degeneration.

In our presentation this morning, Dr. Eli Peli, distinguished low vision specialist and vision scientist, will discuss the disease, the visual problems that it creates, and will also describe the IMT device itself and how it works.

Dr. Stephen Lane, a cornea specialist, a study investigator, will describe the surgical procedure for implanting the device.

Dr. Judy Gordon, a regulatory advisor and

consultant to the company, will present the study design for the two IMT trials, the IMT-002, the pivotal study, a two-year study, and IMT-002-LTM, or long-term monitoring, which provides an additional two-year follow-up on the patients implanted in the pivotal study.

Dr. Doyle Stulting, a cornea specialist and investigator, will present the data from the trial covering both efficacy and safety data.

Dr. Oliver Schein, our third cornea specialist and investigator, will then discuss suggested risk reduction alternatives, especially surgical risks related to the IMT implantation, and conclude with a risk benefit analysis.

All of our presenters will be available to answer questions. In addition, we have with us today, Dr. Hank Edelhauser from Emory University, an expert in the field of morphology morphometry of the endothelial cells.

We have Dr. Janet Wittes, a statistician known to many of you here in the FDA for her work on clinical trial design and services on FDA Advisory Committees and the National Eye Institute Data Safety Monitoring Boards.

And finally, Dr. Yi-Jing Duh, our

statistician from clinical trials.

All individuals I've just mentioned are paid for their services and expenses, including the services and expenses related to this meeting.

At this time, I'd like to introduce Dr. Peli. Eli.

DR. PELI: Thank you. Good morning. I'm Eli Peli. I'm a vision scientist at the Schepens Eye Research Institute and a Professor of Ophthalmology at Harvard Medical School.

My major research interest in the past 25 years has been visual impairment and its rehabilitation. I also practice visual rehabilitation and see patients at Tufts Medical Center or Hospital where I serve as an Adjunct Professor of Ophthalmology at Tufts School of Medicine.

This morning, I'm going to discuss the manner in which end-stage macular degeneration compromises visual acuity and explain how the Implantable Miniature Telescope significantly improves patient's vision despite the damage done by the MD.

End-stage AMD results in central vision loss associated with geographic atrophy or disciform

scar involving the fovea. The geographic atrophy in dry AMD and the disciform scar in wet AMD are evidence of the central retinal damage. Once the dry or wet scars are present, vision in those areas cannot be restored. So the patient is past the point where -- or other therapies can restore their vision.

The result is a central vision loss. When the lesion include the fovea, there will be a hole in the images the patient can see. The hole, as it is, is not perceived as such and is not perceived as illustrated on this diagram. It's simply not being seen but it can readily be documented with perimetry.

Outside of this hole, the rest of the visual imagery is blurry since it falls in the near periphery where the natural resolution and contra sensitivity of the visual system is reduced.

As was mentioned before, removal of mild cataract and implantation of a IOL will allow for better contrast in the retinal image, but the effect is relatively small and cannot compensate for the loss of central vision in the way that magnification does.

The Implantable Miniature Telescope is an optical prosthesis. It is implanted in one eye to provide central vision function -- and detailed

vision. The fellow eye maintains peripheral vision for navigation.

The IMT consists of two microlenses that together magnify the retinal image of the object. Magnification have two effects. One, it allows the undamaged area outside the macular lesion to see the image by increasing the size of the details to match the capability of the visual system -- Two, it minimizes the relative size and thus the impact of scotoma or the scar.

There are two IMT models, 2.2 and 3X. The 3X actually, in part 2.7X magnification. The depth of field is extending from 1.5 meter beyond which is ideal for intermediate distances activity. Addition of -- spectacle allows the patient's implanted eye to be used for near tasks such as spot reading, identifying items in the grocery stores, not just the wife, and playing cards or doing crafts. The 3X and 2.2X IMTs provide 20 degrees and 24 degrees field of view respectively. These fields of view are appreciably greater than those provided by conventional external handheld or spectacle mounted low vision telescope, the best of which provide about 14 degrees field of view.

This is a depiction of a realistic size

macular scar, about 1.5 disc diameter, in letters of a size about 1 degree, that will be barely readable for many of these patients. For example, an eye chart. The patient may be able to see that there are letters, but in order to know what letters they are, the patient has to get them first outside of the scarred area, where in this slide, it shows on the scar area, onto the functional retina.

The patient with AMD indeed uses a place on the retina called the preferred retina locus or PRL, as seen on the right side, but without magnification, the resolution of the retina at the PRL will be inadequate to see what the letters are. On the left side of this slide, you see the last slide we just seen without magnification. On the right side, we illustrate what happens with the IMT in place. The letters are now enlarged about three times, and at that size, the patients have an image in the functional area of the retina, large enough to allow him or her to be able to recognize what the letters are.

Again, with the magnified image, the relative size of this scotoma is smaller, making it easier to keep the object of interest, at least most of it, outside of the scotoma.

I want to take a minute to add my rehabilitation hat to my vision science hat. Like many of you, I have trained many patients how to use external telescope. Now I have also had the opportunity to consider how the two devices will compare.

The IMT has a number of advantages over the external telescope. One of them is the wide affected field of fixation of the IMT. The IMT allows scanning using natural eye movement rather than head movement. With an external telescope, eye scanning is limited to the small field of view that even with the largest telescope is very small. To scan beyond this, head movements are needed. These are much slower and, as discussed next, cause a significant problem when interacting with a vestibular mechanism.

With the IMT, the scanning, the natural eye movement, is not limited by the field of view of the telescope and does not cause a problem with the vestibular system. So there's no vestibular conflict. I'll take a minute to address this topic.

When working or sitting in a vehicle, the head is constantly moving and bobbing. To maintain stable fixation and thus stable retina image, the vestibular mechanism in the inner ear compensates for

these movement by counter rolling the eye at the same angle that the head rotated. This can be seen on the left side, looking at the eye without the telescope. If the head turn by angle -- and the eye will turn back, then the image will return to the fovea.

With an external telescope, however, the movement of the head by the same angle results in a magnified, amplified image movement in the retina three times. And then when the eye rotates back, it only rotates for the one -- and as a result, the image sweeps back only slightly across the retina, and there's no vestibular compensation or almost none. In this case, two-thirds only is not compensated or a third is only compensated.

This results in reduced acuity and unpleasant image motion that may cause motion sickness.

With the IMT, which is shown on the right side, this problem disappears as the normal vestibular reflex brings the image back to the fovea and avoid -- motion and vestibular effects.

Importantly, the IMT is available on demand; that is, it is always there ready to use. There's no need to locate it, to bring it to the eye, and no need to tie up the hands.

Because it is not visible to anyone with whom the patient interacts, the IMT does not stereotype the patient as visually disabled. And the IMT is compatible with easy social interaction. It allows eye contact, which is crucial, and for many patients, face recognition and recognition of facial expression, which is also crucial in social interactions.

In summary, the IMT is designed to provide improvement in visual acuity to patients whose end-stage AMD has reduced visual acuity to the point where the patient suffers severe -- visual loss. The IMT in effect works around the area of macular lesion to allow visualization of images by sections of the retina that have not been destroyed by the disease.

As you will hear from others, the clinical trial, it improved visual acuity by an average of 3.4 lines. That improvement allows patients to see better which in turn afford them more freedom to participate independently in many tasks that the rest of us take for granted. Thank you very much.

DR. LANE: Good morning, and thank you, Dr. Peli. Distinguished Panel, I'm Stephen Lane, and I was an investigator for the IMT study 002 and the IMT 002-LTM study.

I've implanted 19 of these devices, and I'm going to provide a surgical overview to you this morning.

As Dr. Peli mentioned, there are two models of the IMT. Those models have the same dimensions and are similar in weight, approximately 60 milligrams in the -- which is about the quarter of the weight of the crystal and lens. The anterior and posterior length of the device is 4.4 millimeters, similar to the thickness of the crystal and lens, but as you can see, appreciably larger than the standard intraocular lens, and thus the implantable telescope requires a larger incision, approximately 12 millimeters as compared to the relatively small 2 to 4 millimeter incisions that we use with standard foldable intraocular lenses in cataract surgery today.

The IMT is designed to be placed in the capsular bag. The angulation of the haptic displaces the device posteriorly keeping the bag taut, as you can see here, and provides positional stability, centration, and allows adequate clearance between the device and the corneal endothelium.

In addition, the square edge of the posterior optic and the large surface area of contact

between the optic and the capsule minimizes the potential for posterior capsular opacification. The anterior surface of the device extends through the plane of the iris by approximately half a millimeter.

In this brief video, key components of the procedure will be demonstrated. After a -- has been performed, a 12 millimeter grooved incision at the limbus and a paracentesis are performed, and then a capsule rhexis at a minimum of 6.5 millimeters but ideally 7 millimeters and even a little bit larger, is performed, allowing placement of the intraocular lens easily within the lens capsule. The anterior chamber is entered, and a phacoemulsification is carried out through the small incision as well as clean up of the cortex in the typical fashion that we would typically do with cataract surgery.

Now a dispersive OVD is placed again to protect the endothelium, and the wound is open to the extent of the 12 millimeters in this case using a microscissors. It's important that this really be 12 millimeters. And then by lifting the cornea without tenting it up and without bending it too greatly, the lens can be placed. Additional OVD is placed in a soft shell technique to provide space maintenance, and then a dispersive OVD is placed on the device

itself. It's important, because microcracks can occur, that this be handled very delicately by holding onto either the bridge or to the haptic itself, and then while lifting the cornea, the lens is placed as atraumatically as possible, putting the inferior haptic in the bag and trying to avoid endothelium touch, and then it is rotated to a 6 o'clock and 12 o'clock position using two micro hooks through the incision which aids in the stability of the lens within the lens capsule.

The wound is then closed using multiple interrupted sutures, and the residual OVD is removed using a bimanual irrigation aspiration technique, and then finally at the conclusion, a small peripheral iridotomy is performed using micro instrumentation. A -- injection of methylprednisolone is typically given or betamethasone along with the topical antibiotic as the procedure is concluded.

I think there are a number of very important steps in the procedure that I would like to just briefly summarize and emphasize to you.

First is proper wound construction. It's important that the wound be a minimum of 12 millimeters to allow as big a space as possible to place the large lens.

A capsule rhexis of 7 millimeters is very important. This allows easier positioning of the device into the lens capsule because of the slight stiffer nature of the haptics in this particular device.

Appropriate OVD use to coat the endothelium and to provide space maintenance during the procedure is critical.

Lifting the cornea without folding and tenting it and inserting the device at pretty much a 45 degree angle, as you can see here, to avoid the touch that can occur, is very important to minimize the risk of corneal touch.

And then minimizing intraocular manipulation, placing the loops in the capsule or bag and rotating the haptics to 12 o'clock and 6 o'clock also aids in the stability, and then, of course, careful attention to the wound integrity at the conclusion to maintain the anterior chamber.

This is a photograph of a patient approximately six weeks postoperatively. You can see a well-healed wound, the IMT in good position, and a slight protrusion of the optic through the pupil into the anterior chamber.

Thank you very much for your attention, and

I'd like to now turn the podium over to Dr. Gordon.

DR. GORDON: Thank you, Steve. My name is Judy Gordon, and I am the regulatory consultant to VisionCare.

Protocol IMT-002 was a prospective, multicenter clinical trial, designed to evaluate the IMT for the improvement of visual acuity in subjects with bilateral, stable, untreated, moderate to profound central vision impairment arising from end-stage age-related macular degeneration or Stargardt's macular dystrophy.

Eligibility criteria for protocol IMT-002 may be found on pages 10 through 12 of our executive summary and will not be repeated in their entirety. However, key inclusion criteria are shown on this slide.

The diagnosis of bilateral, stable, untreatable AMD was confirmed by baseline fluorescein angiography. Moderate to profound vision loss was defined as baseline distance visual acuity of 20/80 to 20/800. All study subjects were required to have a cataract, and adequate peripheral vision in the fellow eye was required to ensure that the patient could navigate after implantation of the IMT.

Screening of both eyes with an external

telescope was performed, and patients needed to have an improvement of at least five letters with the external telescope for enrollment. Finally, the protocol required patients to have an anterior chamber depth of 2.5 millimeters on A-scan.

Patients with endothelial cell density of less than 1600 cells per millimeter squared were excluded from enrollment as were patients with a variety of ophthalmic disorders as shown on this slide.

The schedule of visits in the IMT-002 study is shown here. In addition to the scheduled visits, study subjects returned for IMT training under the direction of a low vision professional at the study site at weeks 1, 2, 4, 6, 10 and 12. Each study visit included a complete ophthalmic examination and specular microscopy was performed using non-contact Konan units at off sites. Specular images were analyzed centrally by the specular microscopy reading center at Emory University.

Briefly turning now to Protocol IMT-002 Long Term Monitoring, which we also call LTM, this study was originally intended to be the postapproval study designed to provide long-term follow-up, but VisionCare decided to conduct this trial before

approval with the thought that it would provide additional data on which approval could be based.

Patients in the LTM study were examined at months 30, 36, 42, 48, 54 and 60. Because many patients had not reached their 54 or 60 month visit at the time of data lock, we report data through 48 months in our presentation.

The parameters evaluated at each visit are shown on this slide.

Demographic and baseline information for the IMT-002 and the IMT-002-LTM populations are summarized here. The two study populations were similar at the preoperative baseline. Mean age was approximately 75 years, and the majority of patients in both populations were Caucasian. Mean baseline BCVA was also similar for the 002 and LTM populations at 20/312 and 20/307 respectively.

Accountability is shown on this slide. Protocol 002 enrolled 218 subjects at 28 clinical sites. One subject cancelled surgery resulting in a cohort of 217 operated eyes. As a result of surgical complications, 11 subjects were not implanted with the IMT, leaving a cohort of 206 IMT-implanted subjects.

For the remainder of our presentation, we

refer to the cohort which underwent surgery, whether or not they received an IMT as the operated eyes. The subjects who were implanted with an IMT are referred to as the IMT-implanted eyes.

VisionCare made repeated extensive efforts to enroll in the LTM study all subjects who participated in the IMT-002 study, and 129 subjects were enrolled. Most of the subjects in this LTM or long-term monitoring study did not enroll until after the window had passed for the 30-month visit. Of the 85 subjects enrolled by 36 months, 84 were available for analysis. At 48 months, 106 of 123 were available for analysis. Reasons for discontinuation included death, loss to follow-up, and one IMT removal.

Dr. Doyle Stulting will now present the effectiveness and safety outcomes for these studies.

DR. STULTING: Thank you, Judy. I'm Doyle Stulting. I was an investigator for this study, implanting 15 of the study eyes. I will be discussing efficacy and safety results.

The primary effectiveness endpoint for the IMT-002 study was an improvement at 12 months of two lines or more in either near or distance best-corrected visual acuity in 50 percent of the

implanted eyes.

The secondary effectiveness endpoints were improvements in visual function, quality of life, using two different questionnaires, the VFQ-25 and activities of daily life.

I'm going to begin with visual acuity. Improvements in visual acuity exceeded the primary effectiveness endpoint for the trial. At 12 months, 90 percent of IMT-implanted eyes and 88 percent of all operated eyes had at least a 2 line gain in either near or distance vision, exceeding the 50 percent specified as the primary endpoint.

Those gains were maintained at 24 months for all operated eyes and those implanted with the IMT. Patients implanted with the 2.2X and the 3X models achieved about the same results.

For all IMT-implanted eyes at 12 months, 70 percent improved 2 or more lines in both near and distance acuity, 50 percent gained 3 or more lines in both, 80 percent of subjects gained 2 lines or more of distance visual acuity, 66 percent gained 3 lines or more, 45 percent gained 4 lines or more, and 25 percent gained 5 lines or more.

The gains in best-corrected near vision were similar.

Overall, there was a mean improvement of 3.4 lines of best-corrected distance vision at 12 months. The mean best-corrected distance vision improved from 20/312 at baseline to 20/141 at 12 months and 20/149 at 24 months.

Improvements in near vision were similar.

We also looked at improvements in each of the three baseline distance vision groups, 20/80 to 20/160, 20/160 to 20/400, and worse than 20/400. All three groups met the two line endpoint criteria. The effect was greatest in eyes with the worst baseline vision.

In addition to these comparisons to baseline, we were also able to compare the IMT-implanted eyes to fellow eyes. As you can see in this graph, many more implanted eyes gained lines of distance vision at 24 months than did fellow eyes, and fewer implanted eyes lost visual acuity.

The fellow eye data show a normal distribution with a similar number gaining or losing visual acuity at two years. The distribution of the IMT eyes shows the majority of patients with improved vision.

During the LTM trial, subjects maintained significant improvement in best-corrected distance

vision compared to baseline levels. At 36 and 48 months after IMT implantation, approximately 70 percent of LTM subjects had a 2 line or greater improvement in best-corrected distance vision, and approximately 50 percent had a 3 line or greater improvement. Mean best-corrected distance vision improvements were generally retained at 36 and 48 months in IMT-implanted eyes.

Consider what an improvement in 3.4 or even greater lines of visual acuity would mean to a patient performing activities of daily life. I doubt that any of the people with end-stage macular degeneration who undergo IMT implantation will ever be able to drive. Some of them though will be able to read a newspaper. Some of them who were unable to recognize their grandchildren across the room will be able to do so, and some whose spare time was previously occupied with arts and crafts will be able to again enjoy those activities. Even a simple activity of watching television from across the room may again be possible.

As you heard from the previous speakers this morning, there's no question that the IMT makes a difference in the lives of its recipients: reading when it was impossible before, making turtles for the

neighbors, and not stepping on the cat.

We use two objective assessments of quality of life to measure the impact of the IMT. The first is the NEI visual function questionnaire using the 25 item version. The second is the activities of daily life survey.

The VFQ has 25 items which are divided into 12 subscales. Each is measured on a 100 point scale. For any subscale, and for the overall composite score, changes of 5 to 10 points are clinically meaningful. Three subscales, those for general vision, near activities, and distance activities, are important for daily living. For these subscales, scores improved by 14, 11, and 8 points, respectively. Also dependency improved by 10 points, social functioning by 9 points, and role difficulties by 7 points. Other subscales for ocular pain and driving were generally unchanged. As expected, because of the way the IMT limits peripheral vision, the peripheral vision subscale decreased by 6 points. General health declined by 5 points probably for reasons unrelated to vision as seen in other studies in this age group.

The overall score, which includes all vision related items but excludes general health,

increased by 6 points at 1 year.

The results of the activities of daily life assessment were similar.

We also looked at whether the improvement in visual acuity could have resulted from cataract removal rather than implantation of the IMT. There are several analyses demonstrating that cataract extraction did not account for the improvements that we saw in visual acuity.

First, the mean cataract density in the implanted eyes estimated by the investigators was 2 plus. Clinical experience suggests that removal of such a cataract would not result in improvements in visual acuity in this experimental population of patients with end-stage macular degeneration.

Physicians, I among them, usually advise end-stage macular degeneration patients that removal of a mild cataract and placement of an IOL might improve problems with glare but that it will not improve central acuity.

Recall that mean improvements in IMT-implanted eyes in this study was 3.4 lines, an improvement appreciably greater than one would expect from a 2 plus cataract in patients who are legally blind or near so.

There are three sources of data from the study to allow us to evaluate the potential contribution of cataract removal.

First, we can look at visual acuity in a cohort of fellow eyes that underwent cataract removal and IOL implantation. In these 22 eyes, mean improvement in vision was .35 lines or 2 letters on the ETDRS chart.

Second, there were eyes in which cataract removal was performed with implantation of IOL rather than an IMT because of intraoperative complications. In this group of 9 eyes, mean improvement at best-corrected distance vision was .38 lines, again two letters on the ETDRS chart.

These changes of approximately half a line are minimal compared to the mean gain of 3.4 lines in the IMT eyes.

When comparing the 22 fellow eyes that underwent cataract extraction and IOL implantation during the study, it is apparent that the difference between the proportion of eyes that gained 2 or more lines and those that gained 3 or more lines is very large.

Patients with bilateral end-stage macular degeneration implanted with the IMT experienced

meaningful gains in visual acuity. Quality of life also improved at a clinically meaningful level.

Let me now turn to safety. Safety outcome measures for this study was best spectacle-corrected visual acuity, endothelial cell density, complications, and adverse events.

At 12 months, 5 percent of eyes lost 2 or more lines of near or distance vision without a corresponding gain in the other. At 24 months, the rate was 6 percent.

Since we measured visual acuity in fellow eyes, we know the impact of the underlying macular degeneration on our study population. More than 10 percent of the non-implanted fellow eyes lost more than two lines of best-corrected distance vision by 36 and 48 months of follow-up, which is significantly greater than that seen in the IMT-implanted eyes.

Eleven eyes were not implanted with the IMT due to surgical complications. Five of these aborted cases, three capsular ruptures and two choroidal detachments that occurred before IMT implantation was even attempted. In six cases, operative complications occurred during the insertion of the IMT, including four cases of capsule rupture, one case of zonular dehiscence and one case of suspected,

but not actual, choroidal hemorrhage. The IMT was not implanted in these eyes and instead an intraocular lens was placed of standard design.

Those of you who are familiar with modern IOL implantation might think that these rates of capsule rupture during IMT implantation are high, and you are correct. In fact, we became aware of this increased rate of capsule rupture during the clinical trial. This was related to the relative stiffness of the IMT haptics compared to those of traditional implants.

As Steve mentioned in his presentation, the investigators quickly learn techniques for implantation that reduced the rate of capsule and zonular damage during surgery.

There were eight IMT explants during the clinical studies. Two devices were explanted early in the study as a result of device failures, cracks in the cylinder and condensation within the IMT. These device failures may have been due to improper handling of the device. After additional physician training and modifications of the manufacturing process, the problem did not recur.

Two were removed during corneal transplantation for the treatment of visually

significant corneal edema.

Eight IMTs were explanted at the request of the patient because of dissatisfaction. Of these eight, four subjects had an improvement in best-corrected acuity, two had no change in acuity, and two eyes had a loss of best-corrected acuity. Interestingly, 3 of these dissatisfied subjects were among the 6 study subjects with Stargardt's disease, while the other 5 were among 200 patients with macular degeneration.

To explain this significant tendency for Stargardt's patients to be dissatisfied with the IMT, we hypothesized that these patients have learned to use their peripheral retinas over their lifetime experience with a hereditary retinal disease as opposed to patients with macular degeneration who acquired their disease later in life.

Thirteen cases of persistent corneal edema were observed during five years of follow-up. One of those eyes did not receive an IMT because of surgical complications. Of the 12 eyes with an IMT, edema resolved in 3 eyes, 7 lost vision due to corneal edema, 4 of these underwent corneal transplantation, and 3 had no further intervention.

This slides shows details of the eyes that

underwent corneal transplantation. As you can see, in each case, there were complications during the initial surgical procedure causing rapid loss of endothelial cells. In three of the four cases, endothelial cell density prior to transplantation was 300 to 500 cells per millimeter squared. In the fourth, there was a secondary surgical intervention before transplantation was required. In two cases, the IMT was removed during transplantation, and in the other two, it was left in place.

The outcome of corneal transplantation in these eyes was good.

Posterior capsule opacification was noted in 12 eyes, but it was not visually significant in 11 eyes. There was one case of visually significant posterior capsule opacification. Capsulotomy in this case was performed by a pars plana approach without complication, and vision improved from 20/726 to 20/320, just as we might expect with a traditional intraocular lens implant. There were no reports of retinal detachments or endophthalmitis.

Since the cornea is curved and the IMT is cylindrical, one might wonder how much clearance there is between the IMT and the mid periphery of the cornea immediately above it.

Here we see the distance from the edge of the IMT to the cornea stratified by the preoperative anterior chamber depth measurement in the 45 eyes for which ultrasound biomicroscopy or OCT images were obtained. In these subjects, there was good clearance at the right and left mid periphery of the cornea.

Implantation of the IMT does restrict the ability to visualize the retina. However, the retina can still be examined. Although fundus photographs or imaging with other methods was not required by the protocol, at the request of FDA, fundus photographs were collected from clinical sites that have obtained these from IMT-implanted eyes. Investigators were also asked whether fundus examinations had been routinely performed and whether there had been any difficulties in visualizing the fundus.

Fundus examinations could not be performed in four percent of the 1800 examinations that were attempted, forcing angiography, diagnostic photography, OCT and/or B scan ultrasonography was successfully performed in almost all of these subjects whose retinas could not be examined by direct visualization.

Investigators reported use of a contact

lens aided examination in eyes with unsteady fixation.

Endothelial cells are responsible for maintaining corneal clarity. Normal eyes have been reported to lose about .6 percent of their endothelial cells each year, and we know that corneal clarity is maintained until the endothelial cell density reaches a level of about 3 to 500 cells per millimeter squared. Endothelial cells are lost acutely during routine cataract surgery, but the remaining endothelial cells are sufficient to maintain corneal clarity in most cases.

Before this clinical trial began, we selected a target of 17 percent endothelial cell loss at 1 year. The actual endothelial cell loss was 25 percent. Were that rate of loss to persist, many patients would develop corneal edema within their lifetimes. But that initial rapid rate of loss did not persist in the IMT studies.

After the initial surgical loss, the chronic later rate of endothelial cell loss was slow, about three percent per year. This biphasic pattern of endothelial cell loss is the same as the pattern reported by Bourne and others following traditional cataract surgery.

Another measure of endothelial cell health is morphology. As you can see in these slides, there is a decrease in percent hexagonality immediately following surgery with subsequent recovery to preoperative levels.

There is also a barely perceptible change in coefficient of variation.

The data on endothelial cell loss associated with IMT implantation are consistent with what has been seen with other cataract surgical procedures. As reported in the literature and shown on this slide, surgical loss following procedures involving larger incisions are associated with higher rates of postoperative endothelial cell loss.

For intracapsular cataract surgery, the 12 month endothelial cell loss is 22 percent, and for extracapsular surgery, the lose ranges from 9 to 17 percent. Chronic loss for extracapsular procedures is reported by Bourne to be 2.8 percent per year, which is quite close to the IMT's 3 percent rate of chronic loss.

Endothelial cell loss was 19 percent in non-IMT-implanted fellow eyes that underwent cataract surgery during this study, using modern techniques and small incision, clear cornea surgery.

Thus, the observed 25 percent endothelial cell loss produced by IMT implantation is slightly above that reported in the literature after large incision cataract surgery and after routine small incision surgery in this elderly population of patients with macular degeneration.

In this study, we had a unique opportunity to determine the rate of endothelial cell loss following routine cataract surgery in these elderly subjects with macular degeneration. This slide shows the chronic endothelial cell loss in fellow contralateral eyes that had cataract surgery with traditional intraocular lens implants in their non-steady eyes.

For the period between 12 and 24 months, there was no difference in the rate of endothelial cell loss in the IMT-implanted eyes and pseudophakic fellow eyes, about 3 percent for both. This is consistent with a chronic rate of 2.8 percent following cataract surgery reported in the literature by Bourne.

Let us return to our measurements of safety. More than twice as many fellow eyes lost two or more lines of best-corrected acuity than did IMT-implanted eyes. So this criterion was clearly met.

There is a 25 percent acute loss of endothelial cells, as you might imagine, having seen the implantation procedure presented by Dr. Lane. This is 5 percent more than that seen after large incision surgery with implantation of traditional IOLs in reported series, and only 6 percent more than we observed in fellow eyes of subjects undergoing cataract extraction with modern, clear cornea incisions during the clinical study.

This acute loss is followed by a much slower chronic loss of 3 percent per year, which is no different from that seen in fellow eyes undergoing cataract extraction using modern techniques during the course of the study. Primarily as a result of surgical complications, 3.3 percent of study eyes went on to develop visually significant corneal edema.

Complications and adverse events which we did not discuss in detail today are listed in the written Panel summary and are similar to those seen after traditional cataract surgery.

We conclude that the clinical trials of the IMT provide valid scientific evidence of efficacy and safety, and we conclude that the benefits exceed the risks in this elderly population of patients who are

legally blind from a progressive degenerative retinal disease with no currently available treatment.

Thank you. I'll turn the podium over to Dr. Schein.

DR. SCHEIN: Good morning. My name is Oliver Schein, and I'm a corneal specialist from the Wilmer Eye Institute at Johns Hopkins. I was also a study investigator.

First, I'd like to say that I agree with Doyle, that the benefits of the IMT exceed its risk in the overall study population. And I'll be discussing some idea for how to further reduce the risk of endothelial cell density loss or ECD based on data from the two studies.

These risk reduction strategies are likely to reduce ECD loss as a consequence of the surgery and provide a means to maintain ECD at a level needed for healthy cornea during the patient's lifetime.

VisionCare evaluated a series of factors known or thought to be relevant to endothelial cell density for their contribution to loss of ECD in the entire IMT-implanted population. These included chronic inflammatory reactions, contact lens wear, history of diabetes or glaucoma, iritis greater than 30 days in duration, pigment deposits on the IMT and

anterior sneaky eye. And no statistically or clinically significant differences in ECD were found for patients with these factors.

Other factors, however, did have an effect on ECD loss at the three-month postoperative period, specifically the presence of guttata, the depth of the anterior chamber, and surgeon training.

Corneal guttata are a well-known risk factor for ECD loss following cataract surgery and the same effect was seen in the IMT-002 study as demonstrated here.

Anterior chamber depth less than 3 millimeters was also a risk factor. There is less working space in these eyes, and considering the size of the IMT, it makes sense for candidate patients to have deeper anterior chambers.

Surgeon specialty also made a difference. Subjects whose surgery was performed by a corneal specialist experienced a 13 percent loss of endothelial cell density at 3 months compared to 21 percent by non-corneal specialists.

The sponsor has taken into account these three issues, guttata, anterior chamber depth, and surgeon specialty, by proposing labeling that deals with all three of these risk production strategies.

Here's what implementation of these straightforward risk reduction strategies will help to do. At three months, the patients without guttata and with an ACD of 3 millimeters or greater lost an average of about 170 cells per square millimeter fewer than those with guttata and an ACD less than 3 millimeters, and this advantage was clearly maintained over time.

Adding the effect of surgery by a corneal specialist further reduces the risk of ECD loss at surgery. ECD loss is lower by approximately 200 cells per square millimeter in eyes with guttata, shallow ACD, or implantation by a non-corneal specialist.

Thus, the fully risk-reduced cohort arrives at three months, or the end of the postoperative period of greatest cell loss, with a mean ECD of approximately 200 cells per square millimeter higher than the mean ECD of all other eyes in the cohort. Starting the long-term period of postoperative and age-related endothelial cell loss from a higher base should certainly be an advantage since a higher ECD level after surgery should postpone the risk of a low ECD by many years as shown in this model projection in front of you.

Now I recognize, as does the sponsor, that these kinds of risk-reduction strategies are based on a relatively small number of subjects and were arrived at by post hoc analyses. In this context, however, that does not appear to me to be problematic. When one is analyzing efficacy data, there are methodologic problems with post hoc analysis, principally the appearance of finding a treatment effect that is not, in fact, present.

Here there is no such methodologic issue. Unless the risk-reduction strategy would, in fact, increase risk, and there is no reason to think that that is the case here, finding a risk-reduction strategy is at a minimum neutral, at best highly desirable, and certainly makes commonsense.

The presence of corneal dystrophies such as guttata are commonly known to increase the risk of ECD loss in anterior segment procedures. Increasing the minimum required anterior chamber depth increases the working space for cataract removal and the implantation of the device. And corneal specialists are skilled in and comfortable with procedures involving large corneal incisions and related wound management.

There's one more approach that can be

implemented to help ensure long-term corneal health. The sponsor has proposed a risk-reduction strategy designed to help guide the surgeon and patient in making the decision to proceed with IMT implantation. This is done by means of a decision grid which utilizes preoperative ECD, the patient's life expectancy, and the prediction of ECD loss based on a combination of four-year patient data and conservative estimates of long-term endothelial cell loss.

There is a precedent for this strategy. An ECD decision grid is currently employed in the labeling for phakic intraocular lenses.

To build the grid, we specified a minimum of 750 endothelial cells per square millimeter at the end of life. We believe that 750 is a reasonable and conservative threshold because eyes in the range of 500 to 750 typically do not have vision loss from swollen corneas. We used standard estimates for life span for men and women at various ages.

And the question we want to answer is how much endothelial cell density a patient needs to have at the time of implantation to stay at or above 750 throughout his or her life span? That depends, of course, on the assumptions you made first about the

rate of surgical loss and second about the annual rate of loss.

For both the surgical rate of loss and the subsequent annual rate of loss, we built the grid using values from our predictive model with date through 48 months. Given person-to-person variability, and to be more conservative, for the annual rate of loss, we used not the predicted mean but rather its upper 90th percent confidence bound which is 6.2 percent per year.

Under this assumption, here are the minimum ECD values prior to implantation various patients must have to provide a minimum ECD of 750 cells per square millimeter throughout their lives.

So as you can see in this example here, a 70-year-old male would need to have at least about 2200 cells per square millimeter prior to implantation based on those assumptions.

If you recommend, as I do, to use the ACD and guttata risk-reduction strategies, then you can slightly reduce the pre-implantation ECD required because of the ECD sparing properties of those strategies. Under that assumption, as shown in this slide, a 70-year-old male would need to have about 2,000 cells per square millimeter prior to

implantation.

Certainly one can debate about the best or the most appropriate grid, but both of the grids I have shown or any potential grid will certainly inform surgeons' and patients' decisions about the ECD needed prior to surgery to maintain ECD levels higher than 750 over a patient's life span.

None of the grids that I have showed you has incorporated the lower levels of ECD loss anticipated when surgery is done by a corneal specialist. That layer of prediction is in addition. No sulcus fixation is also listed as implantation inside the capsular bag assures both better fixation of the device and additional clearance from the cornea.

I would like to close by putting the IMT in a clinical perspective that makes sense to me as an anterior segment specialist who has become very familiar with the device and the data.

First, where are candidate patients likely to come from? Almost certainly they will come from retinal and low vision specialists who will refer patients with bilateral central vision loss from AMD whom they know are frustrated with their vision and are interested in exploring the full range of low

vision options.

Second, patients will be evaluated by low vision specialists who will determine that the patient responds to a standard external telescope. Practically speaking, patients with improved vision with an external telescope, but have difficulty applying or sustaining its use, are the ones who will likely be referred, or at least the subset of such patients that the low vision specialist believes will be able to participate adequately in the post-surgical low vision training period.

Finally, when such patients are referred to me, I will have a frank discussion of the surgical risks and benefits. The chief benefit is an excellent likelihood of achieving three or more lines of improvement in vision. The principal risk is loss of corneal clarity resulting in a loss of more than two lines of vision or corneal transplant. Using the entire IMT cohort, that risk was about 1 in 30 over a 5 year interval. If the patient has an adequate ECD per the grid, and I choose patients with adequate anterior chamber depth and without guttata, I can feel quite comfortable that the patient will live his or her life with improved visual acuity and quality of life without ever falling below the critical level

of endothelial cell density.

In summary, implanting the IMT in patients with end-stage age-related macular degeneration, with moderate to profound vision loss, confers gains in vision and quality of life that are clinically significant, and their benefits exceed their risk. Thank you.

DR. WEISS: Is this concluding the sponsor's presentation?

MR. HILL: Yes.

DR. WEISS: Thank you very much. We will now open up to the Panel members to ask the Panel members if they have any questions for the sponsor. Also, the Panel can understand that there's going to be opening to ask the sponsor questions later on. Yes, Dr. Eydelman.

DR. EYDELMAN: Dr. Weiss, I just wanted to bring Panel members' attention to two slides in the sponsor's presentation that contain the analysis. We're not aware whether it was submitted in official amendments to the PMA. Hence, we cannot verify their validity at this time. Unfortunately these slides aren't numbered, but specifically the two slides were in Dr. Stulting's presentation. One is entitled % ECD Loss After Cataract Surgery, and it's the 19

percent that's circled in red, and the following slide entitled Pseudophakic Fellow Eyes: Chronic ECD Loss of 3 percent.

DR. WEISS: Thank you. I just want to, yeah, I want to localize them, and I guess we all need to localize them. So could you just show that to us, or would it be easier for you to present the two slides that Dr. Eydelman is --

MR. HILL: Let me just address, that the reference to the 14 percent loss and 19 percent loss was provided in the executive summary. I believe that's something on page 46 of the booklet you have. I won't be quite right on that, if someone cares to look at that. So these were again contralateral fellow eyes that had cataract surgery and IOL implant. So that information was submitted.

DR. EYDELMAN: Could you please clarify whether it was submitted in the official amendments to the PMA?

MR. HILL: Yes, I believe it was, Malvina.

DR. EYDELMAN: Okay.

MR. HILL: We don't have the volumes in front of us.

DR. EYDELMAN: Okay.

MR. HILL: As it relates to the

pseudophakic fellow eyes, annual rates of loss, previously submitted to the FDA. I'll find the amendment.

DR. EYDELMAN: Thank you.

MR. HILL: There are rates of pseudophakic fellow eyes at the onset of surgery or at the onset of implant, or prior to the enrollment. That has been previously submitted to the FDA. I will find that.

DR. EYDELMAN: Thank you.

MR. HILL: All right.

DR. WEISS: The entire PMA is here. So it might be beneficial, and the Panel will just star these two, but if you can find where the amendment is --

MR. HILL: We will do our best.

DR. WEISS: -- then we can include that.

MR. HILL: Yes. Thank you.

DR. WEISS: And for everyone on the Panel, what we're looking at or the slides in question, the top of the page is % ECD Loss After Cataract Surgery, that slide was included, but the slide that we're referring to is the slide underneath with the yellow highlight, and from what I understand, the next page, on the top of the page, Pseudophakic Fellow Eyes:

Chronic ECD Loss.

Does anyone on the Panel have a question for the sponsor? Dr. Higginbotham. And also for the benefit of the transcripts later on, can everyone from the Panel, when you make a comment, give your name into the microphone so it will be easy for them to identify.

DR. HIGGINBOTHAM: Eve Higginbotham. I was impressed by the difference in outcome between corneal specialists compared to non-corneal specialists, and certainly the impact of the ACD, the anterior chamber depth, as well as the guttata in terms of patient selection was also quite striking. So my question is whether or not corneal specialists were less likely to choose patients who had guttata and AC depth that was rather small? So is it a matter of patient selection or technique that one needs to tease out here?

DR. WEISS: And if you can also identify yourself, Steven.

DR. LANE: Sure. Steve Lane. I can only speak for myself, but I certainly did not pre-choose patients based on corneal guttata. I think this was all data that was determined in the analysis that came out, and certainly patients who had end-stage

guttata or guttata were certainly not chosen I think probably by anybody, but in terms of my own personal selection of patients, it had nothing to do with the preoperative counts that were obviously counted each time preoperatively. So we looked at the endothelial cell modulator in making our decisions about surgery, but certainly there were no determinations, at least on my part. I can't speak for Doyle or any of the other investigators.

DR. WEISS: Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: Thank you.

MR. STULTING: May I continue the answer to that last question?

DR. WEISS: Sure. Doyle.

MR. STULTING: I'm Doyle Stulting. These patients came to us after being screened by the retinologist and the low vision specialist, and I personally did not exclude anyone. So there was no selection on our part, and I think I speak for all of the surgeons. I think the difference probably between the outcomes from corneal specialists and those from other implanters was the training and the ability to handle the cornea in a way that avoids endothelial cell damage.

These are large implants. The surgical

technique is very different than it is from modern intraocular lens implantation. Some training is necessary, and I think that would be part of the postmarket plan.

DR. WEISS: Doyle, I have a question again with the corneal surgeons. I guess all of us are probably wondering, is there a confounding variable? I think that's what you're getting at. Now, as a corneal surgeon, of course, I know corneal surgeons do it better, but I'll put that aside for the moment.

Let's say the largest implanters of the device, the top five implanters, were they all corneal surgeons?

MR. HILL: Allen Hill. No.

DR. WEISS: So there wasn't a correlation between the number that were done and the fact that the individual's a corneal surgeon who implanted it?

MR. HILL: There is a correlation, not necessarily statistically significant correlation between experience. The more cases you do, the better you get, the lower the cell loss. One of the interesting things was in the analyses of the data, that was called a training effect, was not present for corneal trained specialists. I think that largely drives what we're seeing in the data.

DR. WEISS: So that the corneal surgeon didn't need to do five before they hit their stride. Their first five were similar to their later cases?

MR. HILL: That's in general correct, yes.

DR. MATOBA: Might they have been older surgeons who had done extracaps or even one or two intracaps, you know, early on in their training?

MR. HILL: No offense --

DR. MATOBA: That occurs to me having been in that category.

MR. HILL: No offense to the surgeons and our advisors, but all of them have gray hair.

DR. WEISS: Before or after implanting the device? Sorry. That was Dr. Matoba asking the question.

DR. MATOBA: Yes, sorry.

DR. WEISS: And I'm going to give everyone else a chance. We're going to stay on this question. So anyone who has a question about the corneal surgeon part, I'd like to stay on this aspect of it, and Dr. Stulting's going to answer that aspect, and if any other Panel members want to proceed with other questions on this particular topic, then we'll go onto another topic. Dr. Stulting.

DR. STULTING: To address Dr. Matoba's

question about gray hair, I have a little but not a lot yet. I would comment that during the implantation procedures, it was my thought that people who had had experience with large incision surgery would probably be much more familiar with it. Certainly surgeons that are going through training today don't get this kind of experience, and that's a very good question.

To address another of the questions, whether corneal surgeons happen to be selecting patients, I'd also like to comment that certainly in our institution, these patients came to us through the retinal service. None of them were my patients before the IMT implantation was recommended. So there was really no filtration by the anterior segment surgeons. These were mainly people who resided in retina practices and low vision practices before they came to us.

DR. WEISS: Does anyone else on the Panel have a question specifically about the corneal surgeon aspect. Otherwise, if not, we'll -- yes.

DR. SUNNESS: This has been very helpful and enlightening for understanding the study. I'm Janet Sunness.

The issue of endothelial cell loss and your

calculation of it is obviously critical to the safety of the IMT. And in the graphs you provide of endothelial cell loss over time, the initial IMT study itself includes all eyes, and obviously the LTM study only includes those LTM eyes, which is about a half or so of the total population. And what I was wondering is if you looked at just the eyes that you had in the LTM, and you did the same kind of analysis, what would be the endothelial cell loss because it's possible, for example, that the cohort in the LTM study had either higher ECD on levels at baseline or a lower rate of declining, and that would affect how we look at this.

MR. HILL: Allen Hill. Dr. Sunness, in regard to the, take the group, the population that enrolled in the long-term monitoring trial, which in total was about 129 patients as compared to the patients who did not enroll, in terms of all baseline characteristics, they were very much the same. One small difference, maybe it's not so small, that you should be aware of is that at three months postop, the patients in the LTM study did have a higher ECD loss. We followed that from three months throughout all of available data. The rates of loss for that group are comparable to the number we have for all

patients, all available data, that was presented. There are tables, various tables that represent that data in our submission.

So I think I can say without any hesitation, the rates of loss for that population, whether you include or exclude the non-LTM patients, are comparable.

DR. WEISS: Karen.

DR. BANDEEN-ROCHE: I have some data elaboration questions which might not be necessary to answer right now. I don't know if it's possible to look up some of them. I had the same question as Dr. Sunness, and I suppose I also missed that table. If you could direct us to the relevant information, that would be helpful.

So three aspects. In terms of the effective, the IMT versus cataract surgery, it would be helpful if you could comment on the relative baseline acuity for the control versus the IMT eyes. So I'm getting at how comparable were the control on the IMT eyes in terms of the change that might have been expected?

The second question goes to the safety outcomes of the loss of best-corrected distance vision as well as corneal edema. Are there any

accumulative incidents analyses, you know, something like a Kaplan-Meier that accounts for censoring? So that's a second question.

And then finally, in terms of the decline in endothelial cell density, the model, the biexponential model, you know, is an elegant, seems like a very reasonable model. But two aspects: It would be very helpful to see the actual fit of that model to the data, you know, so that if there's anything sort of providing a plot of the data with respect to the fit of the model. And then finally, the model assumed independence of the observations. I know that's the way it was in the original paper, but the problem with that is that the confidence bounds could well be invalidated, and so I'm just wondering whether any analyses that tried to account for lack of independence was conducted, for instance, using a robust variance correction. Thank you.

DR. WEISS: If the sponsor has any answers to any of those questions, you can supply those, or if it's something that needs to be looked up and supplied later.

MR. HILL: Yes, we'd like to take a little bit of time to --

DR. WEISS: Come back and speak to us about

that.

MR. HILL: -- provide the answers in a comprehensive fashion.

DR. WEISS: No problem. You will have that time. Alice.

DR. MATOBA: I have two questions. The first is regarding the eight patients who chose to have their implants explanted. You said they were merely dissatisfied, but I just wondered, do you have any more insight into why they chose to undergo another procedure to remove it. If they were merely dissatisfied, it just seems drastic that they would want another procedure. And could you give us follow-up as to what the endothelial cell loss was after the second procedure and how they did with follow-up after the explantation?

MR. HILL: Allen Hill. Regarding the reason for the explants, the primary reason was a statement of displeasure due to glare, that type of thing. In individual discussions with the investigators regarding these patients and low vision specialists that were managing these patients during the training period, we recommended various glare mitigation strategies. Some of these patients who voiced displeasure just did not go along with things