U.S. FOOD AND DRUG ADMINISTRATION

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OPHTHALMIC DEVICES PANEL
OF THE
MEDICAL DEVICES ADVISORY COMMITTEE

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OPEN SESSION

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FRIDAY,
JULY 14, 2006

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The above-entitled matter convened at 8:00 a.m. in the Montgomery Ballroom of the Hilton Washington D.C. North, 620 Perry Parkway, Gaithersburg, Maryland, William D. Mathers, M.D., Chair, presiding.

PRESENT:
WILLIAM D. MATHERS, M.D. Chair
NEIL M. BRESSLER, M.D. Member
RICHARD BRILLIANT, O.D. Temporary Voting Member
RICHARD T. BUNNER Consumer Representative
STEPHEN A. BURNS, Ph.D. Member
TIMOTHY B. EDRINGTON, O.D. Member
FREDERICK FERRIS, M.D. Temporary Voting Member
MICHAEL R. GRIMMETT, M.D.Temporary Voting Member
BARRETT G. HAIK, M.D. Temporary Voting Member
DALE K. HEUER, M.D. Member
ANDREW J. HUANG, M.D., M.P.H. Member
MARI PALTA, Ph.D. Temporary Voting Member
JANET S. SUNNESS, M.D. Temporary Voting Member
JANET SZLYK, Ph.D Temporary Voting Member
JAYNE S. WEISS, M.D. Temporary Voting Member
MALVINA B. EYDELMAN, M.D. Director, Division of Ophthalmic Devices
SARA M. THORNTON Executive Secretary

FDA PRESENTERS:

KESIA Y. ALEXANDER, Ph.D.
Chief, Intraocular and Corneal Implants Branch

JAMES F. SAVIOLA, O.D.
Chief, Vitreoretinal and Extraocular Devices Branch

EVERETTE T. BEERS, Ph.D.
Chief, Diagnostic and Surgical Devices Branch

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:48 A.M.)

CALL TO ORDER

DR. MATHERS: It's 8:45. Please take your seats.

And I would like to call this meeting to order. This is the Ophthalmic Devices Panel.

My name is William Mathers. I am the acting - I am the chair of this ophthalmic devices panel, and I note for the record that the voting members constitute a quorum as required by 21 CFR Part 14.

And I would like to remind public observers at this meeting that while this meeting is open for public observations, public attendees may not participate except at the specific request of the panel.

At this time I'd like to have the panel introduce themselves. And shall we start with Malvina?

DR. EYDELMAN: I wanted to welcome all of you here again.

DR. MATHERS: We're going to go around and introduce the panel members at this time.

DR. EYDELMAN: Malvina Eydelman, Division

Director of the Division of Ophthalmic and Ear, Nose and Throat Devices, FDA.

DR. FERRIS: I'm Rick Ferris. I'm the Director of the Division of Epidemiology and Clinical Research, and the Clinical Director at the National Eye Institute.

DR. SZLYK: I'm Janet Szlyk, and I'm the Director of Low Vision research at the University of Illinois at Chicago Department of Ophthalmology and Visual Sciences.

DR. HAIK: I'm Barrett Haik, Chairman of Ophthalmology at the University of Tennessee and at St. Jude Children's Research Hospital.

DR. BRILLIANT: My name is Richard Brilliant. I'm an optometrist and Associate Professor at the Pennsylvania College of Optometry. My specialty is low vision. I'm the Director of the Moore Eye Foundation.

DR. SUNNESS: I'm Janet Sunness. I'm Medical Director of the Hoover Services for Low Vision and Blindness at the Greater Baltimore Medical Center, and I'm a specialist in medical retina and low vision and clinical vision testing and electrophysiology.

DR. BRESSLER: Neil Bressler. I'm at the Johns Hopkins University, a Professor of Ophthalmology

there, and Chief of the Retina Division there.

DR. BURNS: I'm Steve Burns, Professor of Optometry, Indiana University.

DR. HUANG: I'm Andrew Huang. I'm Professor of Ophthalmology, University of Minnesota, Director of Corneal Services there.

MS. THORNTON: I'm Sara Thornton. I'm with the Division of Ophthalmic and ENT Devices at FDA and Executive Secretary for this panel.

DR. EDRINGTON: Tim Edrington, Professor of Optometry, Southern California College of Optometry.

DR. HEUER: Dale Heuer, Professor and Chairman of Ophthalmology, Medical College of Wisconsin in Milwaukee.

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

DR. GRIMMETT: I'm Michael Grimmett. I'm in private practice in Jupiter, Florida. I'm a cornea and external disease subspecialist.

DR. PALTA: Maria Palta. I'm Professor of Biostatistics and Population Health, University of Wisconsin, Madison.

MR. BUNNER: I'm Richard Bunner. I'm the Consumer Representative to the panel. I'm a board

member of Prevent Blindness America, Chair the Government Affairs Committee, and am retired from the Ohio Department of Health.

MS. NIKSCH: I'm Barbara Niksch. I'm the Industry Representative.

DR. MATHERS: And as I said before, I am Bill Mathers, a Professor of Ophthalmology at Oregon Health Sciences University and a specialist in cornea and external disease.

And I would like to pass now to Sally to give us some remarks on conflict of interest.

MS. THORNTON: Before I do that, Dr. Mathers, I'd like to continue with the introductions, and introduce to the panel and to the public Ms. Karen Warburton. Hi, Karen.

She will be the person who will assume my position of Panel Executive Secretary upon my retirement in May of next year.

She will be shadowing me until that time, and learning the many facets of this position. I wanted you all to meet her now.

INTRODUCTION REMARKS

MS. THORNTON: Continuing with my opening remarks, I do wish you a good morning on behalf of the FDA, and I'd like to welcome you to the 109th meeting

of the Ophthalmic Devices Panel.

Before we proceed with today's agenda I have a few short things I wanted to say. I'd like to remind everyone to sign in on the attendance sheet in the registration area, which is just outside the doors of the room.

All public handouts for today's meeting are available at the registration table. Messages for the panel members and FDA participants, information, or special needs should be directed through Ms. Ann Marie Williams, who is available at the registration area.

The phone number for calls to the meeting area is 301-977-8900.

The FDA press contact for today's meeting is Dr. Malvina Eydelman.

The September 19-20, 2006 tentatively scheduled panel meeting has been cancelled. Information on the November 23, 2006 meeting will be available in late August.

In consideration of the panel, the sponsor, and the agency, we ask that those of you with cell phones and pagers and any other noise making devices either turn them off or put them on vibration mode while in this room. And please make your calls

outside the meeting room.

Also, I'd like to call the panel's attention to the questionnaire that's in their folder today. We would like you to fill this out. Show and tell. We'd like you to fill this out and return it to committee management with your travel vouchers after you go back home. And we'd appreciate 100 percent return on these. Thank you very much.

Lastly, will all the meeting participants please speak into the microphone, and give your name clearly initially so that the transcriber will have an accurate recording of your comments.

Now I'd like to read the appointment to temporary voting status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27th, 1990, and as amended August 18th, 1999, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for this meeting on July 14th, 2006: Dr. Richard Brilliant; Dr. Frederick Ferris; Dr. Michael Grimmett; Dr. Barrett Haik; Dr. Mari Palta; Dr. Janet Sunness; Dr. Janet Szlyk; and Dr. Jayne Weiss.

For the record these individuals are special government employees or federal employees and

consultants to this panel or other panels under the Medical Devices Advisory Committee.

They've undergone the customary conflict of interest review, and have reviewed the material to be considered at this meeting.

This is signed, Dr. Daniel Schultz, director of the Center for Devices and Radiological Health, dated 6-15-2006.

Now I'd like to read the conflict of interest disclosure statement.

For the Ophthalmic Devices Panel of the Medical Devices Advisory Committee, date of the meeting, July 14th, 2006:

The Food and Drug Administration (FDA) is convening today's meeting of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Act (FACA) 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 USC 208, are being provided to participants in today's meeting, 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 USC 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 outweigh his or her potential financial conflict of interest.

Members and consultants of this panel who are special government employees at today's meeting have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their employer, spouse, or minor child related to the discussion of today's meeting.

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

Today's agenda involves the review of a premarket approval application, or PMA, for a visual

prosthetic device which, when combined with the optics of the cornea, constitutes a telephoto lens, and is indicated for use in patients with bilateral stable macular degeneration, and other bilateral stable untreatable central vision disorders.

This is a particular matters meeting during which specific matters related to the PMA will be discussed. 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 USC Section 208(b)(3) to Doctors Neil Bressler and Dale Heuer for their employers' interests in the sponsor's study.

The waivers involve a grant to their institutions. They had no involvement in data generation or analysis.

Dr. Heuer has management responsibilities over study investigators. Both institutes received less than $100,000 in funding for the study.

The waivers allow these individuals to participate fully in today's deliberations. A copy of these waivers may be obtained by visiting the agency's website at www.fda.gov/ohrms/dockets, d-o-c-k-e-t-s, /default.htm, or by submitting a written request to the agency's Freedom of Information Office, Room 630

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.

This statement can also be found on the web at http://www.fda.gov/ohrms/dockets/default.htm.

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

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 special - 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.

DR. MATHERS: We will now proceed with a presentation from Dr. Aron Yustein to present the FDA award to Jayne Weiss.

FDA AWARD PRESENTATION

DR. YUSTEIN: Thank you, Dr. Mathers.

My name is Ron Yustein. I'm the clinical deputy director for the Office of Device Evaluation in the Center for Devices and Radiological Health here at FDA.

And this morning I have the distinct honor of representing the agency in presenting an award of recognition and appreciation to Dr. Jayne Weiss for her outstanding service as panel chair to this Ophthalmic Devices Advisory Panel.

As most of you know Dr. Weiss is a world-renowned refractive and corneal surgeon, professor of ophthalmology and pathology at Kresge Eye Institute at Wayne State University in Detroit.

Her affiliations are way too numerous for me to list here, but include being on the board of advisers for the Eye Bank Association of America; being part of the AAO's committee on research, regulatory and scientific affairs; the board of directors of the Cornea Society; and she's also currently serving as the chair of the International Committee for the Classification of Corneal Dystrophies; I think I got that right.

Dr. Weiss began her career here at the FDA back in 1999, and in 2000 became a standing voting

member of the Ophthalmic Devices Panel, and then in 2002 became the chair of this panel, and remained in that role up until her last meeting I believe back in 2004.

During that time she led the panel on various novel devices, including Wavefront guided LASIK, accommodative intraocular lenses, and Phakic IOLs.

Throughout all that time she remained very enthusiastic; showed a great deal of professionalism; and dedication to the mission for public health service that we value here at FDA.

So with that, I'd like to read a letter from the Office of the Commissioner.

Dear Dr. Weiss: I would like to express my deepest appreciation for your efforts and guidance during your term as a member and chair of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee.

The success of the committee's work reinforces our conviction that responsible regulation of consumer products depends greatly on the experience, knowledge and varied backgrounds and viewpoints that are represented on the committee.

In recognition of your distinguished

service to the Food and Drug Administration I am pleased to present you with this enclosed plaque, and that is signed sincerely yours, Randall W. Lutter, Ph.D., associate commissioner for policy and planning.

And I'd like to present that plaque to you. And I'll read that for everybody since most people cannot see it.

It says: U.S. Food and Drug Administration, advisory committee service award presented to Jayne S. Weiss, M.D., chairperson, in recognition of distinguished service, Ophthalmic Devices Panel of the Medical Devices Advisory Committee, Center for Devices and Radiological Health, from November, 2000 to October, 2004.

So Dr. Weiss.

(Applause)

DR. WEISS: Well, thank you very much.

I was trying to think this morning, how long have I been doing this? 1999, that's a long time, but it's been enjoyable, and I very much have appreciated the privilege - and it's been a privilege - of being able to serve as a member of this panel, and more recently, as its chair.

And the reason it's been a privilege for those of you who are less familiar with the work of

the panel and this particular division, is, the members of the agency are particularly committed. And it's been wonderful to meet and work with the members of this division, from the late Dr. Ralph Rosenthal, who did a great job, to the new division chief, Dr. Malvina Eydelman, who I know is going to continue her commitment to excellence and do a great job with the division.

I also want to express my thanks to the directors and chiefs of the branches of the division, Dr. Saviola, Dr. Beers and Dr. Alexander, and also thanks to the other members of the agency, who work with us as panel members and make our job much easier, and particularly Dr. Bernie Lepri, Dr. Don Calogero, and Gene Hilmantel.

And a particular thanks to Sally Thornton, who is actually both the right and left hand of the panel chair, whether or not all panel chairs are willing to admit this, I will in public.

Finally, it's been a pleasure to get to meet and work with other members of the panel. These are doctors, vision scientists, from all different types of expertise who share the idealistic notion of trying to distill down the boxes and volumes and volumes that panel members get, to try to take the

pure scientific truth from these data points in order to determine which devices will best serve the American public.

And I think all the panel members that I have met have been committed to this goal, as I have been as well.

So I appreciate the opportunity to have been able to serve with the panel and work with you all, and I particularly value your acknowledgement, and the plaque will have a position of honor on my wall.

Thank you.

(Applause)

DR. MATHERS: We'll now hear from Malvina Eydelman to give the division updates.

DIVISION UPDATES

DR. EYDELMAN: Good morning once again and welcome.

Since our last ophthalmic public meeting held in March of 2004, the Division of Ophthalmic and ENT Devices has undergone many changes in our staff.

Unfortunately, as most of you know, this January, DOED mourned the passing of Dr. Ralph Rosenthal who directed our division from 1996 to March of 2005.

It was a great loss for all of us who had the honor of working with Ralph during his FDA tenure.

After 29 years at the FDA, our deputy director, Dave Whipple, retired this May. While we all miss him, we're delighted that he's enjoying his retirement.

During the last fiscal year we lost four reviewers due to retirement, and one to a tragic accident.

Even though our division has lost a large percentage of our staff, our workload did not decrease. I'm proud to report that during this difficult transitional period, DOED has been able to complete all of our work within the statutory timeframe.

I want to use this opportunity to publicly thank DOED staff for their dedication, hard work, and a lot of overtime, without which this would not have been possible.

Our division's reputation as having great staff is largely responsible for our ability to recruit many new excellent people.

I will now introduce those who have joined us since the last meeting of the ophthalmic panel.

As of July 2004 Dr. Keisa Alexander -

please stand up wherever you are - became the Branch Chief of the Intraocular and corneal Devices Branch. Dr. Alexander obtained her B.S. in chemistry from University of District of Columbia, and her Ph.D. in analytical chemistry from Howard University.

Dr. Alexander has been with FDA over 10 years. During this time she worked as a chemistry reviewer in the diagnostic and surgical devices branch, as well as in the intraocular and corneal implants branch.

She has served details in the former division of clinical laboratory devices as a chemistry reviewer and branch chief.

Dr. Alexander's role as ICIB's branch chief has been an invaluable additional to our division's management team.

In March of 2005 Dr. Tina Kiang, please stand up, joined the agency as a member of the intraocular and corneal implants branch.

Dr. Kiang has her bachelor's in chemical engineering from Cooper Union, and a Ph.D. in biomedical engineering from Johns Hopkins University.

Her Ph.D. research involved polymer biomaterials with emphasis on controlled release technologies.

Dr. Kiang has been an asset to the division, and we all welcome her.

In May 2005, Ms. Claudine Krawczyk, who is not here, unfortunately, today, returned to our division as part-time reviewer under the Oak Ridge Institute for Science and Education, or ORISE, program.

Ms. Krawczyk has a B.S. and Master's degrees in mechanical engineering from the University of New York. She joined the agency originally in June of `94, as a member of intraocular and corneal implants branch.

She left FDA in October of 2000, and we were delighted to hire her back after her hiatus from the Agency.

In March of this year Dr. Joseph Hutter - thank you - joined our division. Dr. Hutter has a bachelor of science in chemical engineering from the University of Florida, and Master's and Ph.D. from Penn State, all in chemical engineering.

Prior to joining FDA he worked for the U.S. Department of Energy and Argonne National Laboratory in Chicago.

For the last 10 years Dr. Hutter worked as a laboratory scientist in FDA's Office of Science and

Engineering Laboratories, also as most of you know.

During his time in the labs he worked on a variety of medical device applications and forensic investigations, such as dialysis equipment, surgical meshes and other implanted devices.

Over the years Dr. Hutter held various scientific and management positions at OSEL, and we were very fortunate to convince him to join us in the Office of Device Evaluation.

And now for our most recent recruit, Dr. Mark Robboy joined our division this week. So he has four days on the clock.

Dr. Roebuck received degrees in business administration and optometry from Ohio State University. After his undergraduate degree, Dr. Robboy worked as a management analyst for the Ohio State University office of university planning.

After receiving his doctor of optometry degree, Dr. Robboy worked as a research optometrist, senior scientist, and as a manager of a research clinic for a manufacturer of contact lenses and eye health product.

Dr. Roebuck joins FDA after working in private industry for over 25 years.

We look forward to benefiting from his

extensive knowledge in the field of contact lenses.

While this completes the introduction of new staff that is physically here, I'm happy to report that my division is in the process of hiring eight additional staff members. All of these positions are in the final stages of being filled, and we look forward to incorporating all of the additional talents into our expertise.

Thank you, that completes my remarks.

DR. MATHERS: Dr. Alexander to give the ICIB branch update.

BRANCH UPDATES

DR. ALEXANDER: Thank you, Dr. Mathers.

As stated my name is Kesia Alexander, and I'm the chief of the intraocular and corneal implants branch.

As I understand I have about five minutes to go through this, so please bear with me.

I'm going to start off first beginning with PMAs and HDEs that we have approved since the last panel meeting.

The first one was P030023, was approved on April 27, 2004. This PMA is for Ophtec's Oculaid, also known as Stableyes Capsular Tension Rings.

These rings are indicated for the

stabilization of weakened, broken or missing zonules that are suspected or observed during cataract extraction using phacoemulsification and continuous curvilinear capsulorhexis techniques in adults.

Next is P030028 was approved on September 9th, 2004. Again this is for Ophtec's device. It was for their Artisan, also known as Verisyse Phakic Intraocular Lens. This was reviewed by the panel in February of 2004. The lenses are indicated for the reduction or elimination of myopia in adults with myopia ranging from -5 to -20 diopters with less than or equal to 2.5 diopters of astigmatism at the spectacle plane, and whose eyes have an interior chamber depth greater than or equal to 3.2 millimeters in patients with documented stability of refraction for the prior six months as demonstrated by spherical equivalent changes of less than or equal to .5 diopters.

P040020 was approved on March 21st, 2005. This is for Alcon's AcrySof apodized defractive posterior chamber IOL. This IOL is indicated for the visual correction of aphakia secondary to removal of cataractous lens in adult patients with and without presbyopia who desire near, intermediate and distant vision with increased spectacle independence.

The lens is intended to be placed in the capsular bag.

P840064, supplement 26, was approved on March 23rd, 2005. And this is for Alcon's Discovisc Ophthalmic viscosurgical device.

Discovisc is intended to aid in intraocular surgery during anterior segment surgical procedures by maintaining the depth and shape of the chamber and/or capsular bag, offering protection to the corneal endothelium from trauma resulting from contact with surgical instrument or devices being implanted such as intraocular lenses and coating instrumentation.

P930014, supplement 15, was approved September 14th, 2005, and this was for Alcon's AcrySof Single Piece IOL with Toric Optic. The AcrySof Toric posterior chamber IOLs are intended for primary implantation in the capsular bag of the eye for visual correction of aphakia and preexistent corneal astigmatism secondary to removal of a cataractous lens in adult patients with and without presbyopia, who desire improved uncorrected distance vision, reduction of residual refractive cylinder and increased spectacle independence for distance vision.

P010059, supplement 2, is for Morcher

Cionni Capsular Tension Rings. This device is indicated for improved stabilization of the crystalline lens capsule in the presence of weak or partial absent zonules in adult patients undergoing cataract extraction with intraocular lens implantation.

P030016 was approved December 22nd, 2005. This was for STAAR's Visian Implantable Collamer Lens, which was reviewed by the panel October 3rd, 2003.

The Visian is indicated for adults 21 to 45 years of age to correct myopia ranging from -3 diopters to less than or equal -15 diopters with less than or equal to 2.5 diopters of astigmatism at the spectacle plane, to reduce myopia ranging from greater than -15 diopters to -20 diopters with less than or equal to 2.5 diopters of astigmatism at the spectacle plane, and with an anterior chamber depth 3 millimeters or greater, and a stable refraction history within .5 diopters for one year prior to implantation.

We also have one HDE that was approved, and that was H04002, and it was approved on July 26th, 2004. This was Addition's technology INTACS prescription inserts for Keratoconus. INTACS inserts

are intended for the reduction or elimination fo myopia and astigmatism. Inpatients with Keratoconus, who are no longer able to achieve adequate vision with their current contact lenses or spectacles, so that their functional vision may be restored, and the need for a corneal transplant procedure may potentially be deferred.

The specific subset of Keratoconic patients proposed to be treated with INTACS prescription inserts is outlined in the summary of safety and probable benefits.

Next I would like to move on to a brief statement about Toxic Anterior Segment Syndrome, referred to as TASS.

As many of you may have heard, there has been an influx of TASS cases reported in the ophthalmic community. I want to let you know that we are aware of the situation, and that it is currently under investigation.

Lastly I would like to address some staff changes. As Dr. Eydelman mentioned, we had one member of my branch that had passed away, and that was Ms. Susan Gouge who passed away in a car accident last November. Susan had been with the agency since January, 1979, and she was an exemplary

microbiologist, and it goes without saying that she is deeply missed.

And thank you so much.

DR. MATHERS: We will now hear from Dr. Beers to give the DSVB branch update.

DR. BEERS: Thank you, Dr. Mathers.

I'm Everette Beers. I'm chief of the Diagnostic and Surgical Devices Branch.

As far as staff, we were fortunate. We've had no staff changes since the last panel meeting in February, 2004.

We have seven scientific reviewers, one branch chief, and we have a secretary that we share with another branch.

We've had eight PMA approvals since the February 5th, 2004 panel meeting.

The first one was the - actually this panel reviewed the Refractec ViewPoint CK System from Monovision in February, 2004 at that panel meeting.

That was approved March 16th, 2004. The PMA number is P010018, supplement 5.

The indication is for conductive keratoplasty for the temporary induction of myopia from -1 to -2 diopters to improve near vision in the no dominant eye of presbyopic hyperopes, and

presbyopic emmetropes.

VISX received approval in December 2004 for hyperopia, for Wavefront-guided hyperopia plus astigmatism; that was supplement 17.

In March 2005, VISX received approval for Wavefront-guided mixed astigmatism.

In August 2005 VISX received approval for Wavefront-guided high myopia plus astigmatism, high myopia from -1 to -11 diopter MRSE.

In June 2004 Alcon received approval for their custom cornea system for Wavefront-guided myopic astigmatism, up to -8 sphere and up to -4 cylinder.

Just very recently in May, 2006, Alcon received approval for their Wavefront-guided LASIK for correction of hyperopic astigmatism.

And then this past April, 2006 WaveLight Allegretto received approval for conventional LASIK for mixed astigmatism.

DR. MATHERS: Next we will hear from Dr. Saviola, who will give the VEDB branch update.

DR. SAVIOLA: Thank you, Dr. Mathers.

As you heard from Dr. Eydelman, we just recently had two new staff additions to our branch.

In addition we did have several retirements in January, 2006. I'd just like to take a

moment to note those folks.

Dr. Daniel W.C. Brown was a former Executive Secretary of the Ophthalmic Device Panel before Sally took that role. And he served the federal government for over 40 years before he retired.

Dr. Jimmy Chen, one of our branch chemists; Ms. Eleanor McGhee, one of our team leaders; and Dr. Linda Cohen, a medical officer, all had over 30 years of federal service when they retired.

So truly it was a passing of an era when these folks left the division.

Since our last panel meeting in February 2004 we've had three original PMAs approved through our branch.

Vistakon Oasis senofilcon A silicone hydrogel lens, which was P040045 was approved in December 2005, and those are for up to six nights, seven days of extended wear.

In June, 2004, the Euclid system, Orthokeratology contact lens for overnight wear was approved. That was P010062. Ownership of that PMA was subsequently transferred to Bausch & Lomb who markets the system as a Boston Vision Treatment system.

And in September, 2004, P040029 for Dr. John Szabocsik, the JSZ Orthokeratology contact lens for overnight wear was approved. This is the same device as the Euclid system Bausch & Lomb PMA.

To obtain clearance Dr. Szabocsik had referencing rights from Euclid, but he has not yet marketed the product.

The indications for the Orthokeratology lenses are for the temporary reduction of myopic refractive error; up to 5 diopters in eyes with astigmatism; up to 1.5 diopters.

And of course to maintain the Orthokeratology effect of myopic reduction, overnight lens wear must be maintained on a prescribed wearing schedule.

Regarding Orthokeratology, I want to touch on the topic of postmarket activities. Under Section 522 of the Federal Food, Drug and Cosmetic Act, FDA has the authority to require manufacturers to conduct postmarket surveillance on their device.

Working with the Office of Surveillance and Biometrics as the lead office in postmarket issues, we have considered the information available to determine whether postmarket surveillance under Section 522 is necessary to address the concerns about

the use of overnight Orthokeratology lenses in patients under the age of 18 years.

There have been published literature reports of serious adverse events associated with the use of these overnight Orthokeratology lenses in this patient population, and also several incidents of microbial keratitis have been reported through our medical device reporting system.

The agency has issued letters to the two PMA holders and Dr. Szabocsik just noted, Dr. Szabocsik, B&L and Paragon.

Paragon markets the CRT and Quadra overnight Orthokeratology lenses that the panel reviewed in January 2002 and were subsequently approved for marketing in June 2002.

And this gave these firms an opportunity to provide information concerning the issue of overnight Orthokeratology lenses and adverse events.

At this time I'm somewhat limited about what I may publicly disclose about where we are in this postmarket surveillance issue. Nonetheless I wanted to make a statement to assure those concerned that we are pursuing this matter actively.

I also want to touch on the Fusarium outbreak that recently occurred that was associated

with the use of ReNu MoistureLoc marketed by Bausch & Lomb. As everyone may be aware, B&L recalled this product from the market place worldwide in the middle of May, 2006, after reports of fungal keratitis in Hong Kong, Singapore, and finally here in the United States.

We owe a debt of gratitude to our colleagues in the Mycotics Disease Branch at the CDC in Atlanta for their rapid epidemiological investigation into this outbreak.

Also the various state health departments are to be commended for interacting with CDC as they were notified by different doctors of these events.

The domestic events would not have been brought to bear if it weren't for the intervention of the treating doctors who initially notified the respective state health departments, and all these people deserve credit for the prompt reaction to this outbreak.

Many professional organizations, including the American Academy of Ophthalmology and the American Optometric Association also should be commended for their outreach efforts, both to their members to collect event reports, and also for their educational efforts reaching out to patients.

FDA is still reviewing the inspection reports, and we're trying to identify the cause definitively for this event. There are a number of theories that are being explored.

Any further action the agency takes will be based on the final results of these inspections and testings that were conducted.

Regarding what outcome this event may have on the contact lens care industry as a whole in terms of recommended tests and international standards, our current FDA guidelines are based on harmonization with the international standard developed by the International Organization for Standards, or ISO.

The working group that is part of the designated ISO technical committee that develops contact lens-related standards recently convened at a previously scheduled meeting in Switzerland in April 2006.

The current standard, ISO 14729, with microbiological requirements and test methods for products and regimens for hygienic management of contact lenses, was already on the agenda of this meeting for its five-year systematic review.

After discussion of a number of technical points, the working group decided that it would be

more expedient to confirm the existing standard as it was, but then to immediately form a project group to work on revisions to the standard.

I just hope that all members will share the results of member companies, and the group will share the results of their Fusarium related testing as they discuss proposed revisions to the standard.

Regarding silicone hydrogel lenses, in response to the new silicone hydrogel lenses that were recently approved and also those under development, there was concern that the existing four lens groupings that are based on water content and ionic charge do not adequately represent solution interactions for these new materials.

As a result the American National Standards Institute, ANSI Z.80 committee, has discussed this topic at their October 2005 meeting and also their February 2006 meeting.

We are currently working with ANSI on issues related to lens groupings, and we will be discussing this topic at the upcoming August 2006 meeting that will be held in Baltimore.

And finally I want to update the panel on the issue of plano contact lenses. I had previously updated back in 2003 on this.

To bring some closure to the issue of decorative, noncorrective contact lenses that are intended to change the appearance or color of a normal eye for decorative use, I'm pleased to state that on November 9th, 2005, Section 520 of the Food, Drug and Cosmetic Act was amended under Public Law 107-96 to establish that all contact lenses are devices as defined by Section 201(h) of the act. Any decorative contact lenses not currently approved or cleared by the Food and Drug Administration is therefore prohibited from commercial distribution, which includes marketing, dispensing lenses directly to consumers without a valid prescription, as all previously approved lenses are prescription devices.

Again, there are many people in both Ophthalmology and optometry who worked very hard to make this happen, and their dedication to public health and the patient's welfare is to be commended.

Thank you very much.

DR. MATHERS: Thank you, Dr. Saviola.

I would like to now introduce Sousan Altaie to give the presentation on the critical path initiative in medical devices.

CRITICAL PATH INITIATIVE IN MEDICAL DEVICES

DR. ALTAIE: Good morning. I'm Sousan

Altaie, and I'm a critical path representative for CDRH at the Office of the Commissioner.

My job is to make sure that all our critical path projects keep moving forward regardless of them being funded or not.

What I will present to you is the critical path initiative at CDRH, and I will describe to you what is the FDA critical path, and why the FDA's interested, and what are the critical path tools.

And I also will talk about the medical device areas of interest at CDRH, and what are the medical device critical path projects that we are running, and how can you get involved as panel members.

I must say that critical path was not funded at all. Secretary Leavitt got interested in the project in April and we were able to secure a $4.5 million for the critical path initiative in 2007, and the proposal for the funding is around twice as much as that for 2008. So hopefully we'll get funded and keep going with this project.

What critical path is is a serious attempt to make product development more predictable and less costly. If one looks at the development journey of medical products, critical path will cover everything

from prototyping to launching the product, and it will skip the basic research area.

So critical path tools do not cover the basic areas of research, and starts with prototyping.

You might wonder why FDA is interested in critical path. We're interested because we realize the significant benefit of bringing innovative products to the public faster.

We are interested because we have unique perspectives on product development. We see the successes, failures and the missed opportunities.

And finally we are interested in critical path because it will help us develop guidance and standards that foster innovation.

We like to work with the industry, academia and the patient care advocates to modernize, develop and disseminate solutions. These are tools of critical path, and I will talk to you about them a little more in detail.

We use this tool to address scientific hurdles in device development.

Critical path tools are methods and techniques used in three regulatory dimensions, that is, in assessment of safety, the tools predict if potential product will be harmful.

In proof of efficacy, the tools determine if a potential product will have medical benefit.

And in industrialization the tools help in manufacturing the products with consistent quality.

We think of critical path tools as biomarkers, Bayesian statistics, animal model biomarkers, clinical trial design, computer simulations, quality assessment protocols, postmarket reporting, and anything else that you guys or anybody else in the United States can suggest to us to add to this list.

If you'll look at medical devices at CDRH, we have a lot of opportunities to have critical path projects. We regulate anything from the Band-Aids to scissors to glucose monitors to MRIs, CT scans, heart valves and defibrillators. So there is a lot of opportunity.

But I'd also like to get your attention to the differences between the critical path track at devices versus drugs.

In the devices we look at complex components versus pure molecules as drugs. We look at biocompatibility versus toxicology.

We have durable equipment and rapid product lifecycle, versus the short lifecycle of the

drugs, and versus the short lifetime of the drugs and long lifetime of the drug molecules.

We deal with the device malfunctions and user errors versus drug-drug interaction and wrong dosing.

We also review these devices and our studies hinge on bench and clinical trials versus only clinical trials in the drug arena.

And also our regulations are different. We deal with quality system regulations in ISO 9000 and the drugs deal with good manufacturing practices.

So we're quite different than the drugs. And so our journey through critical path is quite different.

The areas of interest at critical path dimensions, we look at device safety tools and we think of biocompatibility databases. We think of the effects of products on disease or injured tissues.

Under effectiveness, we look at surrogate endpoints for cardiovascular device trials. We look at computer simulation models for implanted devices.

Under the industrialization we constantly look at practice guidelines for follow up on implanted devices; validated training tools for devices with a known learning curve.

And these are actually a list of some critical path projects at CDRH. For validation fo biomarkers we are working to qualify biomarkers for personalized medicine in diagnosis and therapy as well as product purity and quality.

For prophylovascular stents, we are working with the Stanford University to develop computer models of human physiology to test and predict failure, even before going into animal or human studies.

For intrapartum fetal diagnostic devices we are working with NIH to develop a clear regulatory path with consensus from the obstetric community.

We also collaborate with NIH on pharmacokinetics and image-guided interventions. We are working with the University of San Francisco to identify barriers to drug diagnostic device codevelopment.

We are working on pathways for statistical validation of surrogate markers, especially in the area of cardiovascular devices.

We are working with the Juvenile Diabetes Research Foundation to accelerate development of closed loop systems using continuous glucose sensors and insulin pumps, linked by a control algorithm.

Our scientists at the Office of Science Engineering Laboratories are collaborating with various researchers to develop animal models and computer simulated virtual families to improve prediction of toxic effects of medical products.

This is actually how you can get involved. In April of this year the commissioner released a critical path report, and it lists the areas that I touched upon at CDRH, and this report lists all the areas in medical devices, and it has also an attached list to it, and it lists all the projects that we think are feasible in doing.

And there is a hurdle in the way of development of those medical devices. And you could actually add to this list, or pick one of the main participating consortiums to address the development hurdles.

At the end I'd like to leave you with this concept: product development has many stages - parts, if you like - and they are all interconnected.

Here at CDRH we believe in ensuring the public health through the total product lifecycle, and we actually think it's everyone's job.

So if you have any questions, I'd be interested to entertain your answers.

Yes.

DR. HAIK: I'm wondering, this has some of the feelings of a road map project from NIH where it transects many different -

DR. ALTAIE: That's correct, and we do try to harmonize with them. We have a lot of projects with NCI, and we're trying to work on their oncology biomarkers and other biomarkers that ease drug development in that arena, and other areas in NIH - and I mentioned two of them for CDRH. And there is quite a bit of them in the other medical devices.

DR. HAIK: And I can see where many of them were also very specific. So did it go the way the road map projects did to where you had RFA, and then you kind of looked at things that were across the board in specific projects and did pilot funding.

DR. ALTAIE: It actually didn't happen that way. Usually government agencies don't talk very well. It was just by coincidence.

We had interest in NIH groups. We'd constantly work with them on different occasions. And their road map came around independently from the critical path.

But we are all scientists, and we think alike, so a lot of projects happen to just be there

for both centers.

DR. HAIK: I think it's wonderful.

DR. ALTAIE: Thank you.

Any other questions? Thank you.

DR. MATHERS: Thank you.

Now we want to hear from Danica Marinac-Dabic.

CONDITIONS OF APPROVAL STUDIES: RECENT CHANGES IN CDRH

DR. MARINAC-DABIC: Good morning, ladies and gentlemen, Mr. Chairman, Dr. Eydelman, distinguished members of the panel.

My name is Danica Marinac-Dabic, and I am the chief of the epidemiology branch at the Office of Surveillance and Biometrics.

I thank you for this opportunity to provide you with an update of the recent changes that occurred here at CDRH in the area of the postapproval studies program.

I know that your last panel meeting was nearly two years ago, and those are the years that we really went through the great postmarket transformation here, and I hope that you will be interested to hear about those developments.

First, I will describe the general principles that should guide us in requesting,

designing and conducting and evaluating the postapproval studies.

I will then summarize the recent postapproval studies program changes at CDRH.

And finally I will give a brief description of how these changes might impact the panel advisory meetings, discussions and deliberations.

Why do we need postapproval studies? As the medical device technology continues to expand, there continues to be a great need to conduct studies to ensure continuing safety, effectiveness and reliability of the medical devices postmarket.

As we translate our findings from the randomized clinical trial settings to the real world environment, very often essential postmarket questions remained to be answered.

For example we want to learn more about longer term performance of implanted devices including the effects of re-treatment procedures, as well as changes to the product.

We very much like to assess the performance of the devices in the community hospitals in broader patient and physician populations.

We also would like to assess how effective

our training programs are. How devices performed in specific subgroups of populations or vulnerable groups of populations.

And finally specific outcomes of concern both real and potential will require careful monitoring especially in the first years as the technology expands.

As we all know conducting the clinical trials is very burdensome and expensive, and certainly the postapproval studies are a valuable tool to do some of those studies in the postmarket setting.

And certainly the final need for the postapproval studies comes through the panel's meetings and deliberations when you, the panel members, give us very valuable clinical insights into the area of devices that is under our review, and we would like to incorporate some of your recommendations into the postapproval studies requirements.

When talking about premarket and postmarket balance, it is very important to emphasize that initial decision about the safety and effectiveness of the device must be based solely on the quality of the premarket data.

Postmarket data should be used to improve our understanding of the risk-benefit profile, or to

disseminate safety information to the clinical and patient communities, and if appropriate, to take regulatory action.

But please remember that post approval studies should not be used for evaluation of unresolved issues from the premarket phase that are important for the initial determination of the device safety and effectiveness.

Just - this is just a reminder, whereas the regulatory basis for our action, this is Title XXI, Section 814, which states that post approval requirements can include continuing evaluation and periodic reporting of the safety, effectiveness and reliability of the devices for its intended use.

This section also states that the FDA must state the reason, and will state the reason for studies for this requirement, and for the studies that we will ask. And this also comes to translation when we formulate our post approval requirements and our postmarket questions.

Also it's important to say here that the FDA may ask for other requirements that are necessary to provide continued reasonable assurance of safety and effectiveness of the devices postmarket.

Of course this legal authority is not new.

It has been in place for many years. But what is new is that here at CDRH in our constant and continuing quest to improve how we conduct business, we have carefully examined the performance of our post approval studies program in the late `90s, specifically from 1998 through 2000 there were 127 PMAs approved at CDRH with 45 CoA orders.

What I forgot to mention is, post approval studies are essentially the studies that you are very familiar with. They're also known as condition-of-approval studies.

And what we have evaluated at this point is that we didn't have - we had very limited procedures to track progress in the results of the studies. We were not happy about the findings. For many of those studies we did not receive the reports from the sponsors, and for those for which the reports were received, some of them were not reviewed. They were not responded to the sponsors. So there was really clearly a lack of interactive communication with the sponsors.

So because as I said we are not happy about those findings we decided to start with the transformation of the post approval studies program. And the first steps toward that transformation was to

clearly define our goals.

And those goals are stated on this slide. We wanted to help assure continued device safety and effectiveness by good post approval studies program.

We also wanted to obtain useful and timely post market information in the real world settings, and also to better characterize the risk profile of the devices; and to add to our ability to make sound scientific decisions.

The key change that had happened during these actually almost two years now, we started with transformation process for this post approval - actually official transfer of the post approval studies program from Office of Device Evaluation to Office of Surveillance and Biometrics began in January, 2005, and essentially in order to work smarter and to maximize our resources, we realized that actually most of our post market experts are in the Office of Surveillance and Biometrics, so we wanted to take more leading role in the evaluation of these studies, and in that way to free up some time to our ODE colleagues so they can focus more on the premarket evaluation.

And certainly the key is the constant communication, because without each other's input, I

think all of this transformation will not lead anywhere.

So the second step that we decided to do is really to develop the automatic tracking system for post approval studies commitment. And we have that in place. All the post approval systems are tracked; they are in one electronic system.

We have that very careful tracking of all the communications with the manufacturers; all the responses; all the reports come in here, they're being evaluated, the responses coming back to manufacturers.

Currently we have 31 post approval studies in this new system.

So as far as the review process the key change as far as the post approval studies program goes is really adding the epidemiologists on the PMA review team.

And you know at this point I would just like to say a sentence or two about the epidemiology group, because you will see us more in this panel.

And I would like to introduce my staff of 15 epidemiologists who are in the Office of Post Market Surveillance. We are mostly physicians with a Ph.D. in epidemiology or doctorates in public health or Masters in public health. And we are a really

committed, dedicated group of professionals, and we are also very fun to work with. We enjoy our collaborations with Vista Vision, and we continue to be very hopeful that they will engage us more in future assignments.

But what our goal is, really, in the whole PMA process to develop so-called postmarket plan.

We review as any other reviewer in the premarket team will review the protocol, with an eye on the postmarket arena, which means we develop - and I will talk about postmarked planning very shortly, in the next slide - but we develop this postmarket plan, which is a plan for us, for CDRH, to follow.

This is not a plan that we prescribe to the sponsor. It will have some elements to it, but this is how we plan to really follow this device when it hits the market.

Basically we lead development of very well formulated and essential postmarket questions. We lead design of post approval studies.

We work very closely with manufacturer in getting those feedbacks back to them so they can get our input in a timely fashion.

We also provide inputs at panel meetings. So you will see if your discussion today leads toward

approving the device, then at that point you might hear an epidemiologist to talk about those things.

If you decide not to approve then you will not see us.

Then we finalized the protocol with sponsor prior to the time of the approval order, which is very essential, because we tried to cut the time from the device approval to the initiation of the post approval study. So we would like to have the protocol ready when the time - when the device is approved.

And we collaborate with our PMA team throughout. So what is the postmarket plan? This is the comprehensive plan for the following up a device once it's approved and what's in the market.

Epidemiology has the lead in developing it; we do that premarket. And then we certainly, if the post approval study is a part of the approval order, then it's going to be part of the plan.

However, that is not enough. We will do MDR analysis throughout the whole post approval process, and provide six month updates to the PMA folks.

Then we will do a literature review and assessment every six months; provide that feedback to the premarket team.

We will explore external databases, which we routinely do AHRQ assessment based on technology assessment databases, ECRI. CDC has some national surveys. If there are any national estimate that will help us answer the questions, we incorporate them really to integrate what is MDR analysis data would show to us.

And again six month updates of this comprehensive approach are provided back to the premarket study.

What postmarket role epidemiologists have: again, I said, all of these things will be followed throughout the postmarket phase, and we will provide timing updates to our ODE counterparts.

In addition, I don't want to spend much time on this, this is a guidance document we developed to help communicate these changes to manufacturers so they would know how to provide the good reports to us, what our requirements are.

We also made it clear that we intend to provide updates to the advisory panels in the future meetings. So if there are significant finding coming out of the post approval study, we would like you, as our panel of experts to know what those findings are, and we will invite also the sponsors to talk about

those.

And again, there might be some other enforcement options, but we hope that there are not that many of those as we continue doing this interactive approach with this whole process.

We certainly took very much care about the least burdensome approach. And we felt that a good investment of our time premarket will pay off in the postmarket arena. We felt that this is really the least burdensome approach that we can take. If we do things right the first time, there is not going to be a need to go back and forth with several submissions and losing the time, valuable time, instead of doing the postmarket studies.

What are the benefits of this change? We really had this very - we set high standards. We would like to have better designed post approval studies. We would like to track all the post approval studies.

And we would like to have more complete postmarket information being collected and organized by Office of Surveillance and Biometrics, and to feed back to the premarket reviewers.

Now what the impact on advisory panel might be? We value your contribution tremendously,

and we would like to tell you that as we review this premarket, we would like to attempt to lay out important post approval health questions to you during the panel meeting.

If your discussions are going toward approving the device, and we have the presentation - we will be having the presentations ready for things like that. We will have epidemiologists who work on this project on the panel. So he will be or she will be available for your questions.

And again during postmarket the FDA or industry will update the advisory panel on what the result of the progress of the studies are.

So because we really value your input, I again would like to reiterate how important it is for us to hear back from you, and to fill out the questionnaires if you haven't, because that will help define our program better and certainly help us prepare the material that we would like to present to you in a much better fashion, and things that you would like to hear from us. And this is our vision for the future.

Important postmarket questions need to be addressed. Studies, postmarket studies, should be realistic and founded in good science.

Studies should be timely, accurate and provide useful information. The post approval studies report that comes from manufacturers should be clearly identified and effectively tracked, and most important, all stakeholders need to be kept apprised about all these changes, and the progress, and I cannot stress enough how important for us postmarket is to be in constant collaboration with our premarket colleagues.

When doing this I think we will have enforcement options. In very rare instances we will use them when we have to use them, but we will try to anticipate all of these things in advance and come up with a good product, and avoid those enforcement options.

So with that I would like to conclude my presentation, and I would like to wish you a successful meeting and good deliberations and a successful outcome of today's panel meeting.

Thank you very much.

DR. MATHERS: Thank you, Dr. Marinac-Dabic.

We have some questions from the panel.

DR. FERRIS: I just have a quick question.

DR. MARINAC-DABIC: Yes.

DR. FERRIS: Is your postmarket

surveillance limited to observational studies, or is there ever a situation where postmarket you could require a randomized clinical trial?

DR. MARINAC-DABIC: We are not limited with the observational study designs. We can do it. And in fact there are a couple of ongoing randomized clinical trials ongoing for other devices.

We try to avoid them when we can because of many issues. Sometimes there are ethical issues, if there is something that is available and approved, and then how you go and randomize patients.

But there is also the burden and the sponsors we hear very often from sponsors this is very burdensome and expensive approach, and we try if we can to use other tools.

And you know we also try to put more emphasis on hypothesis-driven studies, and to make sure that we have clear objectives and clear hypotheses, not just the scripted studies postmarket.

Thank you.

OPEN PUBLIC HEARING

DR. MATHERS: Thank you.

We're now going to move to the open public hearing section of the meeting, and there will be - we believe we have presentations from three people on

this.

These are essentially testimonials.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making, and to ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes it is important to understand the context of an individual's presentation.

For this reason the FDA encourages you, the public, the open public hearing 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, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

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

Each of these presentations will be limited to approximately five minutes.

I believe our first speaker will be Janet Grant. And I would like to invite you either to present at the podium, or you may sit at the table if that is more convenient for you, whatever you would like. It might be easier to sit.

MS. GRANT: Well, I am Janet Grant. And I am here happily today to talk to you about how my implant has changed my whole life.

The one thing that Vision Care has done for us is to bring us here, give us transportation and lodging, the hotel, food. And that's all.

I'm going to try to tell you about three areas of my life that have changed, to make it shorter; but it has changed everything.

My mother and her sister and her brother all had macular degeneration, and I did too. In those days nothing could be done, so I was really happy to take part in this study, no matter what. I thought it would help me, and maybe help my children and my grandchildren and other people years from now.

One of my most important things in my life was reading. I loved reading, and it became difficult to read regular books. It became difficult to read

big print books, and that is one thing that has helped me.

I had a lot of help in this program, how to read again. How to read sentences again. How to read numbers again. And how to make it - I used to read whole sentences when I read without having blindness. And I had to learn how to put the words together and make a sentence. And it has worked out beautifully for me. I can go shopping in the store, and I don't like spices, but I do buy hog meat, you know, all the things that I can see really well and milk, eggs, and so forth.

So I can go shopping, and I can cook, and I can read out of the cookbook now, and that's just a wonderful thing for me, because I can keep on being a mother and a grandmother and a wife.

My next interesting part of my life was painting, and as I was painting I became developing a dimmer and dimmer ability to see whether that was brown or red, whether it was green or blue. And having the same thing about having to get right up close to my face to see what was going on when I wanted to paint.

Today I can paint, and I know red from green and blue, and I can do beautifully with my

artwork for myself.

Now it might not look as good as my old precision artwork, but maybe it's a little more arty and I like it.

My next thing that I really loved doing was cycling. When I had to give up driving a car, I loved to ride my bike. And of course you have to go fast on a bike or you tip over, and I couldn't go fast, because I couldn't see what was going on ahead of me. I couldn't see if there was a rock in the street, or dogs walking, or garbage cans that I might bump into.

So when I got my visual - well, what do I call it - my visual aid, my implant in my eye, I began - I bought a three-wheel recumbent tricycle that had 13 gears and I began riding that tricycle. And I went around the block a few times. Then I went a little further and a little further. Pretty soon I could ride it for about an hour and a half a day. That was when I'd had this implant for two years.

I went back to Michigan in the summer for my vacation, and my doctor saw me. And he said, what's come over you? You're so healthy? You're stronger. Your legs are stronger.

I said, well, I've been riding this bike.

Well, how can you ride a bike? Well, I have this implant. And so he said, well, guess what, you're going to have a new implant. You're going to have a new knee, one you've been begging for for the last five years.

So yes, I have a new knee, too, due to the lens. So my whole life has changed, it really has.

But the most important thing, I guess, I can say, I have six granddaughters. They are all tall and slender. They're all teenagers. They all have long hair.

I had to get right up to their faces in order to see who was who. Just the other day I looked across the room, and one of my granddaughters said to me, oh, granny, look at this. And I looked over at her, and I said, why, it's Esther, I can tell. I could tell the difference between one grandchild and the other.

It may sound silly, but it was very important to me.

I love my new implant. It's changed my life.

Thank you.

DR. MATHERS: Thank you very much.

Can Ed Nungasser approach the podium?

MR. NUNGASSER: Good morning. My name is Ed Nungasser, and I'm glad to be here.

My travel and lodging accommodations were provided by Vision Care.

However, it was so important for us to be here that I and my wife spent several hundred dollars of our money just to be here, because it's very important.

I had my implant put in on July 31st of 2003. On August 8th, my granddaughter was born. I went to the hospital and I could see her, all 2-1/2 pounds of her. It was quite a sensation.

About a month later I went to a soccer game to see my grandson play. He scored a goal. It wasn't his first goal, but it was the first goal I saw him score.

Since then I've gone to numerous sporting events, and could see them. I watched numerous sporting events on television, and it's great.

I can cross busy intersections. I can go up and down escalators. I can walk and feel safe that I see traffic.

I can't drive a car, but I can see where I'm going. And I think it's - I hope you give serious consideration to this, because there's a lot of people

this could help.

Thank you.

DR. MATHERS: Thank you very much for your remarks.

I believe the third presentation will be read into the record by Dr. Stulting.

DR. STULTING: Thank you, Dr. Mathers.

I'm Doyle Stulting, professor of Ophthalmology at Emory University.

My travel here today is paid by Vision Care, and I will be presenting some of the data to you later on today.

I'm here at this time however to read a letter from Susan Primo, one of my colleagues, and a co-investigator, because she was unable to attend today.

It's to Sara Thornton, executive secretary.

Dear Ms. Thornton: I recently served as a clinical investigator for Vision Care's implantable miniature telescope, and will do so for the upcoming second trial.

I have been a specialist in low vision for 21 years now, and received my formal training at the Veterans Administration Hospital, Eastern Blind

Rehabilitation Center, West Haven, Connecticut, under Dr. Robert Perlin.

In my clinical experience the IMT is the first surgical medical option helping visually impaired patients to regain independence and quality of life through enhanced visual acuity and improved dynamic function.

While there are a plethora of external low vision aids, including some impressive electronic devices, the IMT offers my patients a different option that allows for functional possibilities we have never had before.

At first the advantages of an implantable telescope were juxtaposed by my most immediate concern surrounding mobility. Initially this was the case as many patients had difficulty ambulating.

However, after completing the training rehabilitation sessions, this became much less of an issue, and for many patients, not an issue at all.

The other significant concern was aniseikonia, or different image sizes. Again, after several months, the majority of patients didn't express any issues regarding this difference, similarly to those utilizing a contact lens-telescope combination.

While I don't have the physical evidence to back this up, from my other research activities I believe the brain's ability to compensate for these optical phenomena is due to cortical plasticity.

This phenomenon appears to continue well after the in-clinic rehabilitation.

Perhaps future research efforts can be directed toward this area.

The internal placement of the IMT as compared to an external telescope allows for significant increase in visual field with elimination of the ring scotoma commonly encountered with the external telescope.

Because its placement is near the center of the rotation of the eye, this allows patients to continue to eccentrically view virtually eliminating dramatic head movements.

Many patients achieve dynamic function and psychosocial benefits not seen with other modalities.

Hands-free function is a great advantage for daily activities, and the implications on personal relationships and integrating into the community are invaluable.

With all this said, identifying the right candidates for this procedure is key, as is training

and rehabilitation. The process will be one of requiring six to 12 training rehabilitation sessions. Patients should not expect an immediate result.

Once patient selection criteria have been met, and appropriate training received, the IMT will offer an excellent option to enhance the quality of life for my patients.

Respectfully submitted, Susan Primo, OD.

Thank you.

DR. MATHERS: Thank you, Dr. Stulting.

This is an open session, and is there anyone else who would like to address the panel now?

(No response.)

I see no hands. Since there are no other requests to speak in the open panel session, we will now close this portion of the open public hearing.

And I think at this time it would be appropriate to take a short break before we move on to the next section, which will be the sponsor's presentation.

This is scheduled to begin at 10:30. We've actually pretty much stayed on time, so let's begin at 10:30, and we'll close the session now.

Thank you.

(Whereupon at 10:12 a.m. the

proceedings in the above-entitled matter went off the record, to return on the record at 10:33 a.m.)

SPONSOR PRESENTATION

DR. MATHERS: Let's go. I'm going to reconvene our session now.

And this is the sponsor presentation time. And I see that our executive secretary has now entered the room.

This is a presentation from Vision Care Technology. And I believe our first presenter will be Dr. Judy Gordon.

DR. GORDON: Good morning.

My name is Judy Gordon, and on behalf of Vision Care Ophthalmic Technologies, I would like to thank FDA and this advisory panel for the opportunity to present the clinical findings and PMA P050034 for the implantable miniature telescope used in end stage AMD.

Our presenters today are three of the IMT study investigators: Stephen Lane, medical monitor for the overall study, and a cornea anterior segment and refractive surgeon in Minneapolis; Jeff Heier, a retinal surgeon with Ophthalmic Consultants of Boston, and medical monitor for posterior segment events; and Doyle Stulting, a cornea and refractive surgeon at

Emory University.

We will be joined during the question and answer period by Mark Bullimore of the Ohio State University; Hand Edelhauser of the specular microscopy reading center at Emory University; and Yi-Jing Duh, consulting statistician.

Please note that none of the study investigators who participated in the IMT clinical trial including Drs. Heier, Stulting and Lane, has a financial interest in Vision Care as was disclosed in the PMA submission.

Before we go on to the presentation of data, I'd like to just review the indication for use for the IMT.

So the IMT is indicated for use in patients age 55 and older with bilateral stable moderate to profound central vision impairment, with best corrected vision of 20-80 to 20-800.

Patients must have adequate peripheral vision in the eye not selected for implantation.

They must show an improvement of five letters on an ETDRS chart with an external telescope. And they must also be willing to undertake a postoperative program in vision rehabilitation in order to undergo this procedure.

At this point I will turn the podium over to Jeff Heier who will provide background on the indication for use for the IMT and a description of the device.

DR. HEIER: Thank you, Judy.

Good morning, My name is Jeff Heier, and I appreciate the opportunity to be part of this presentation on the PMA for Vision Care's implantable miniature telescope.

As Judy noted, I have no financial interest in Vision Care. However the company is paying my travel and expenses for this meeting.

End-stage macular degeneration affects approximately 60 - 80,000 patients in the United States each year. The majority of these patients are legally blind as a result of central vision loss associated with geographic atrophy or disciform scarring.

As you can see from these simulations of normal central vision on the left - you could advance to the next slide, please - with normal central vision on the left, and the scotoma associated with end-stage macular degeneration on the right.

This is a devastating disease in which central vision can be severely affected.

As would be expected, end-stage macular degeneration has a profound effect on a patient's normal functionality. We got this from the patients who were kind enough to speak with us earlier today.

Obviously activities requiring reasonably good vision, such as driving or reading a newspaper, are very unlikely to be possible.

Even simple acts we typically take for granted - cooking, differentiating medicines, paying bills, or recognizing the faces of friends or loved ones - become extremely difficult and frustrating.

Treatment options for these patients are generally limited to visual rehabilitation with low vision aids such as illumination, magnifiers for reading, and external telescopes.

Unfortunately, a relatively low proportion of patients actually use the low vision devices, and there is generally low utilization of rehabilitation service by this elderly population.

The implantable miniature telescope is an optical prosthesis that in combination with the optics of the cornea constitutes a telephoto lens when implanted. The IMT contains two wide angle micro-lenses that magnify the image onto the retina, minimizing the relative size and impact of the

scotoma.

There are two models: the model WA, or wide angle 2.2X, and WA 3.0X.

It should be noted that the model 3.0X actually imparts 2.8 times magnification.

Important differences between the implantable miniature telescope or IMT and external telescopes is that the IMT provides a wider visual field than external telescopes; allows natural eye movements as opposed to the slow deliberate head movements necessary when using external telescopes; and has a normal cosmetic appearance.

The IMT enlarges the retinal image 2.2 or 2.8 times, reducing the relative scotoma by projecting the image onto a larger portion of the retina, onto normal functioning retina.

In end-stage disease, all or most of the central five degrees is damaged. The IMT utilizes the central 50 degrees, as show in this simulation.

This slide shows the field and visual simulation for an external telescope mounted on spectacles and the IMT. Because of the vertex difference, the field of view of the external telescope is narrow. In contrast, as seen on the right, the field of view of the wide-angle IMT is

considerably larger.

Scotoma mapping and field-of-view measurements were performed on several patients enrolled in the IMT clinical study using a B&L autoplot device. On the left the preoperative map of a scotoma in the study patient at baseline is shown using six and 12 millimeter targets.

The image was then simulated on the right to demonstrate how a scotoma of this size affects vision.

In this same patient perimetry testing with a six millimeter target was performed using a 2.2X external telescope mounted on a trial frame.

The typical ring scotoma expected with an external device is shown as well.

The field of view is approximately 10 degrees, and the scotoma intrudes into the limited visual field as shown on the right.

Testing was repeated in this same patient following implantation of the IMT using the same six millimeter target. With the IMT the field of view is 25 degrees, and the scotoma is minimized on the autoplot, and this can be shown in the simulation on the right.

I want to emphasize that the simulation on

the right depicts the size of the field and is not intended to depict the clarity or quality of the image.

As previously described the implantable miniature telescope provides a significantly larger field of view than conventional external devices. It magnifies images on the retina, reducing the relative size of the scotoma, and allows natural eye and head movements.

At this point Dr. Stephen Lane will discuss the surgical procedure utilized for implanting the IMT.

DR. LANE: Thank you, Jeff.

My name is Steve Lane. I have served as the medical monitor and a study investigator in the clinical trial of the IMT.

I've implanted 20 IMTs in patients enrolled in the IMT clinical trial. I have no financial interest in Vision Care, but the company is paying for my travel and expenses.

The implantable telescope is appreciably larger than the standard intraocular lens, and thus requires at least a 12 millimeter incision as compared to the relatively small two to four millimeter incisions that we now use in standard phako

emulsification with intraocular lens implantation.

The IMT is designed to be placed within the capsular bag. The angulation of the haptics displaces the device posteriorly, as you can see, keeping the bag taut, providing positional stability, centration, and improving clearance between the device and corneal endothelium.

The anterior surface of the device extends through the plane of the iris by approximately a half millimeter.

This to-scale graphic effectively illustrates the dimensional characteristics of the device, and the need to avoid corneal touch during insertion of the IMT into the capsular bag.

It is this surgical procedure that results in an average endothelial cell loss of about 20 percent. The acute surgically induced endothelial cell loss associated with the IMT is actually quite similar to the historical data on large incision cataract surgery that's greater than five millimeters.

This is followed by corneal remodeling and progressively lower rates of cell loss over time.

Consistent with most new surgical procedures, there's a learning curve, generally the first three cases. But surgeons can be trained to

perform the procedure quite safely and effectively.

When positioned correctly, both haptics of the IMT should be in the capsular bag as shown in this schematic.

In this brief video key components of the procedure will be demonstrated. After a conjunctival peristome has been performed, as 12 to 13 millimeter partial thickness incision is made at the limbus. A paracentesis is made at the extremity and a capsulorhexis performed, ideally seven millimeters in diameter.

Following phacoemulsification and removal of the lens material, the incision is enlarged, in this case with micro scissors.

An OBD of a cohesive nature is placed in the anterior chamber to fill the capsular bag and the anterior chamber, and a dispersive OBD is used to coat the endothelium, and also the IMT device.

Damage in the form of micro cracks can be induced due to trauma to the device during handling or manipulation of the lens. And therefore careful handling of the IMT device is critical, with care being taken to grasp the lens by the carrier of the haptic only.

While lifting the cornea maximally but

avoiding undue bending or tenting of the cornea, the IMT device is inserted into the anterior chamber being careful to avoid contact with the corneal endothelium.

This is accomplished by inserting the leading haptic into the capsular bag at approximately a 45 degree angle. The trailing haptic is placed in the capsular bag, and the lens is rotated using two hooks into a 6:00 and 12:00 o'clock position.

Several interrupted ten-0 nylon sutures are then placed across the wound for closure, and the residual OBD is removed using a bimanual technique.

A peripheral iridectomy is performed and the anterior chamber is reconstituted using balance salt to conclude the case.

A subtenons injection of methylprednisolone or beta methasone is given along with a topical antibiotic.

This is a typical ultrasound image of the eye with an IMT implant showing good clearance between the anterior surface of the IMT and the cornea.

Please note that this information was not included in the PMA, and therefore, not previously provided to the panel.

With proper instruction and training, IMT placement can be performed well by anterior segment

surgeons trained in large incision cataract or corneal procedures.

It is important to note that the retina can be visualized through the IMT as shown on this slide, and in my experience, using a Volk lens at the slit lamp, I have been able to identify the posterior pole in all of my 20 patients.

At this point I would like to review the study design of the clinical trial that is the subject of this PMA, Protocol IMT-002, a prospective multicenter trial designed to evaluate the safety and effectiveness of the IMT.

A total of 28 centers participated in the IMT-002 trial. Twelve of the 28 sites were academic centers, while the remaining sites were represented by private, multi-specialty anterior segment and retinal practices, providing a broad spectrum of surgeons implanting the IMT.

In protocol IMT-002 patients were screened for enrollment using the external telescope, first at the clinical site, and then in a home environment. A gain of at least five letters with an external telescope was required for a patient to qualify for enrollment.

The IMT was planned for implantation in

one eye, the eye with poorer vision was selected if either eye had vision better than 20/200.

For patients with vision worse than 20/200 in both eyes, the selection of the eye to be implanted was made by the study investigator and the patient based on the patient's experience with the external telescope trial.

Postoperatively, patients returned for a complete ophthalmic examination at one day, one week, one month after surgery, and then at three, six, nine, 12, 18, and 24 months.

Vision training was required at weeks one, two, four, six, 10, and 12.

All study patients are currently being consented to allow continued follow up through five years.

Key eligibility criteria are shown on this slide. Baseline fluorescein angiography was performed to confirm that patients have bilateral, stable, untreatable, AMD.

Patients were required to have distance best corrected vision of 20/80 to 20/800, and adequate peripheral vision in the fellow eye to allow navigation.

High myopes and high hyperopes were

excluded from enrollment by limiting the baseline manifest sphere to a range from +4 to -6 diopters.

Patients with other ocular pathologies including uncontrolled glaucoma were excluded from participation.

In this study a minimum endothelial cell density of 1,600 cells per millimeter squared was required for enrollment. However, based on the specular microscopy outcomes in this clinical trial, Vision Care has proposed a minimum ECD of 2,000, or alternatively, a grid of ECD based on patient age, and life expectancy for product labeling.

Study methods included measurement of both distance and near vision, which were measured through the best correction using standard ETDRS charts at all study visits.

Quality of life was assessed through 12 months using two instruments: the validated VFQ-25 and Activities of Daily Living questionnaire modified for use in low vision patients.

Specular microscopy was performed using noncontact Konan units, and images were analyzed by a central reading center at Emory University under the direction of Drs. Hank Edelhauser and Bernie McCarey.

A program of training rehabilitation was

required for all study subjects. In the absence of standards for such training and rehabilitation with an implanted telescope, a group of experts in the field, led by Eli Pelli of the Schepens Eye Institute at Mass. Eye and Ear developed a training program described in the study protocol and implemented by low vision professionals at every clinical site.

This extensive training program consisted of gradual vision practice exercises that included activities performed while sitting and walking, and were performed relative to stationary objects and moving objects.

Five fundamental skills were specifically emphasized. These included localizing, fixating, scanning, tracing and tracking.

Training for distance and intermediate activities were included, as well as for reading and writing.

The key safety and effectiveness endpoints for protocol IMT-002 consisted of change in lines of best corrected vision; quality of life questionnaires; endothelial cell loss; and complications and adverse events.

At this time I will turn the podium back to Jeff who will review the baseline and demographic

information as well as the effectiveness outcomes of this clinical study.

DR. HEIER: Thank you, Steve.

Accountability for the study is shown in this slide. As you can see, 218 patients were enrolled in the trial, and 217 patients underwent surgery. One patient withdrew from the study prior to surgery.

As a result of intraoperative compilations 11 eyes were not implanted, leaving a total implanted population of 206 eyes.

Of the 11 eyes that were not implanted, there were seven cases of posterior capsular rupture; two eyes identified as having choroidal detachments; one eye with choroidal hemorrhage, and an eye with loss of zonular support.

I spoke to both of the surgeons who reported choroidal detachment, and while the event was specifically documented as choroidal detachment, in both eyes there was positive posterior pressure and chamber shallowing, but no sign of choroidal detachment was verified, either intra or postoperatively.

One case of choroidal hemorrhage occurred in a particularly long surgery.

Although these 11 eyes did not undergo implantation, there was no visual loss as a result of these intraoperative complications.

Accountability for the 206 implanted subjects was 97.5 percent at 12 months and 95.5 percent at 24 months.

At the time of the original PMA submission in September, 2005, all the study subjects had completed 18 months of follow up, and 75 percent of subjects had reached 24 months.

Safety data, specifically specular microscopy and adverse events with a total study population through 24 months were submitted to the FDA in April 2006 and the accountability for the complete safety cohort at 24 months is 92.6 percent.

The level of accountability in this study was excellent through the two-year follow up, particularly given the age of the population and the level of visual disability.

The demographic and baseline information summarized on this slide are what one would expect from an elderly AMD population. The mean age was 75 years, and included patients as old as 93.

The lower end of the range reflects a small number of Stargardt's patients who were enrolled

in this study.

There was a relatively even distribution of males to females, and the population was largely Caucasian; again, what one would expect in a typical AMD clinical trial.

The mean baseline corrected distance vision was 20 over 312, with a range of 20/80 to 20/800, again, underscoring the extent of the low vision in this population.

By comparison the mean vision in AMD treatment trials is typically in the 20/80 to 20/125 range.

As we look at the effectiveness outcomes for the IMT, I really want to emphasize that this is a group of patients who historically have had very limited treatment options.

Tremendous advances in the field of AMD have occurred over the last several years, culminating with the recent FDA approval of ranibizumab.

Patients with non-exudative disease are taught about vitamin supplementation and diet modification, the result of studies such as the AREDS trial and other clinical trials.

Patients with new onset exudative disease, or recurrent exudative disease now have the hope and

promise of new agents that offer stabilization and possibly visual recovery.

End-stage patients have no such hope. They are often informed, as delicately as possible but with a degree of finality, that there are no surgical or medical options for them. They are strongly encouraged to seek low vision evaluation and care, and they often will seek this.

The IMT, as you will see over the next several minutes, represents a significant improvement in these patients' ability to perform their daily activities, and as such, a significant improvement in their quality of life.

The primary study endpoint of improvement in either distance or near vision of two lines or greater at 12 months in 50 percent of subjects was easily achieved, with almost 90 percent demonstrating two lines or greater improvement.

In fact over 80 percent of subjects achieved three lines or greater improvement.

This remained almost unchanged at 24 months, with 86 percent of subjects achieving this level of improvement in vision.

The full distribution of gains in line of distance vision shows that approximately 60 percent of

eyes had gains of three lines or more as seen here in the yellow, or in the green; 40 percent had gains of four lines or more; and more than 20 percent had five line gains; and even 10 percent of patients had six lines or more gains of vision.

Similarly, substantial improvements were also observed in near vision measured at eight inches as shown here, and improvement was similar at 16 inches, as shown on this slide.

Again the near vision mirroring the gain in distance vision.

Perhaps the most stringent effectiveness outcome in this study is shown on this slide. Approximately 70 percent of patients gained two or more lines of both distance and near vision, and 50 percent of the patients gained three or more lines of both distance and near vision.

As you can see on this slide, the primary effectiveness endpoint was exceeded regardless of age, gender, baseline preoperative vision or IMT model used.

These improvements in visual acuity are due primarily to the magnification produced by the IMT. It is; therefore, appropriate to compare these achieved improvements with the gain predicted by the

magnification.

In essence, how well does adjusted preoperative visual acuity agree with our postoperative results?

The analysis presented on this slide was not part of the PMA submission, so this will not be familiar to the panel since it was not included in the information provided to you by the FDA.

However, since the panel has been asked to comment on actual versus predicted visual improvements, we felt it was important to address this question.

For the 2.2X IMT model, the predicted gain is 3.4 lines as shown here, and patients came within two letters of this at three lines of gain.

For the 3X IMT the predicted gain is 4.3 lines; and again, patients came very close to this prediction.

As might be expected, based on these data, around 50 percent of patients met or exceeded the theoretical gain in visual acuity, and you see those numbers at the bottom.

These predictions were also tested preoperatively in all patients entering the trial using a spectacle mounted external telescope. These

predictions are again validated although the 3X external telescope does not achieve the results of its IMT counterpart, as shown by the difference in these two graphs.

Furthermore, and consistent with our clinical experience, fewer of the patients met the theoretical prediction with the external telescope, and you see these numbers down here at 35 and roughly 19 percent.

Demonstrating visual improvement in our patient population is important. But the true objective of any intervention is to have a meaningful impact on a patient's quality of life.

In order to capture this effect, both the VFQ-25 and an Activities of Daily Life questionnaire were administered to the study population.

The VFQ-25 is a validated quality of life questionnaire developed specifically for the assessment of vision targeted functioning by measuring the impact of vision problems on quality of life.

This outcome is most eloquently described in a Department of Health and Human Services Agency for Health Care Research and Quality Technology Assessment. And if I may, I'd like to read from that.

This outcome measure may be the most

meaningful of all measures. This is because an individual's ability to perform activities of daily living, mood, psychological status, and any adverse events associated with the intervention should, if these changes are meaningful, be reflected by changes in the individual's quality of life.

The VFQ-25 consists of 25 items representing 12 subscales. Questions relate to general vision, near and distance activities, with scoring based on a 100-point scale.

Importantly, the clinical relevance of this questionnaire has been established such that a five to 10 point change in score corresponds to a two to three line change in vision.

Also given the concerns regarding mobility in IMT-implanted patients, it is important that distance activities such as navigating stairs are considered in this series of questions.

Here we see the change from baseline VFQ scores at 12 months. The most relevant subscales, those most expected to benefit from IMT implantation, all demonstrated gains of six to 14 points, and these included general vision and again near and distance activities.

Similar gains were reported for social

functioning, dependency, mental health and role difficulties.

Declines in general health are expected over time in an aging population, and given the optical properties of the IMT, a decline in peripheral vision is expected.

These clinically relevant changes in VFQ scores are significantly associated with the gains in lines of vision. The mean gain in VFQ score was 7.7 points for eyes with a gain of two lines of near and distance vision, and only 2.4 points for eyes without such a gain.

It is also noteworthy that there was no effect of age, baseline vision, or the IMT model on the change in VFQ scores, but females experienced greater improvements that males in the composite score.

Please note that this analysis was not presented in the PMA submission.

This shows a comparison between the benefits of the IMT and a published study conducted at Bascom Palmer in which quality of life was measured before and after low vision rehabilitation.

Although the study was relatively limited, it does offer one of the few comparisons of VFQ

outcomes in a similar population.

The information shown on this slide was not submitted to the PMA, and therefore not previously provided to the panel. However, since the change in the distribution of VFQ scores for questions five through nine has been posed for discussion by the panel, we are providing that information on this slide.

At the top the number of patients who initially reported extreme difficulty or having stopped doing a task at baseline is shown. And you can see, these are the numbers that fell into that category.

For most tasks, including the mobility-related items on the right, around 60 percent of these patients report a change to moderate, little and in some cases no difficulty following IMT implantation.

So in other words all patients were up in these white categories, but after implantation in most categories, 60 percent of patients came into these better categories.

Substantial improvements were also observed in the activities of daily living questionnaire, consistent with those seen on the VFQ.

To summarize these efficacy outcomes, the

IMT has demonstrated clinically significant benefits in a population of end-stage AMD patients.

These are patients who began with profound and severe visual limitations, and the majority achieved meaningful, measurable increases in their quality of life.

Two years following implantation 85 percent of implanted eyes gained two or more lines of either distance or near acuity, exceeding the 50 percent target identified in the IDE study protocol.

Importantly, 60 percent of eyes gained three or more lines of distance or near, and 50 percent of the population gained three or more lines of both distance and near.

These substantial and clinically relevant improvements in vision were reflected in the significant gains in the relevant scales and composite score on the VFQ. Thus in this study not only did patients' vision improve but their quality of life improved.

At this time I will turn the podium over to Dr. Doyle Stulting who will present the safety findings for the protocol IMT-002.

DR. STULTING: Thank you, Jeff.

I'm Doyle Stulting, professor of

Ophthalmology at Emory University. And I was one of the surgeons in the IMT clinical trial.

I personally implanted 15 of the study subjects, and followed all of them postoperatively. This game me an opportunity not only to become familiar with the surgical procedure but also to understand the effect of the IMT on the lives of the subjects and their families.

I have no financial interest in Vision Care. However, the company is paying for my travel expenses to this meeting.

I'm here because I would like to be able to offer this technology to my patients.

Safety measures for this clinical trial included loss of visual acuity, intraocular pressure elevation, complications, adverse events, and change in endothelial cell density.

Here we see the change in lines of best spectacle corrected distance acuity from the preoperative examination to the last available postoperative examination for all patients in the study.

As you can see only two eyes lost two lines of vision, and three eyes lost three or more, totaling 2.5 percent of eyes that lost two or more

lines of best spectacle-corrected visual acuity.

FDA has raised the issue that visual acuity could be analyzed by adjusting for the magnification produced by the IMT. The IMT works because it magnifies the retinal image. So a gain in best spectacle-corrected acuity would be expected on the basis of image magnification alone as mentioned previously.

The question then is how many subjects were not within two lines of the gain predicted by the magnification of the telescope.

Jeff already introduced calculations of visual outcomes based on the theoretical magnification of the IMT and displayed this slide showing what amounts to 3.4 lines of improvement for the 2.2X IMT, and 4.3 lines for the 3X model.

I would like to remind you that this information was not included in the PMA and therefore not previously supplied to the panel.

Although the gain actually obtained approximates the predicted values, the achieved gain does not match them completely.

Jeff also presented the results of gains achieved by the study population with the external telescope, measured during the preoperative

evaluations and displayed on this slide.

Here you see the theoretical gains in visual acuity from the two models of IMT on the left, and the two external telescopes on the right.

The slight differences are due to the fact that the 3X IMT actually produces 2.8X magnification.

Here are the actual measured acuities for both devices. As you have already seen the gap between theoretical and actual performance is better for the IMT than it is for the external telescope.

In fact, more than half of the IMT patients achieved the theoretical best spectacle-corrected acuity, while significantly fewer achieved this goal with the external telescope.

These findings suggest that the theoretical calculation is not directly applicable to this population. This may be due to variability in the size of the scotoma, or the possibility of the progression of atrophic disease over the course of the study, despite our best efforts to enroll patients with stable retinal disease.

Since the theoretical calculation of expected acuity based on the magnification of the telescope does not match the observations in this study with either an external telescope or the IMT,

adjustment of the loss of lines of vision by the theoretical gain is not an accurate or meaningful reflection of changes of vision in this population.

The unadjusted visual acuity values remain the most meaningful analysis of both safety and effectiveness, since they reflect the vision enjoyed by the patient.

There was a transient rise in intraocular pressure after implantation of the IMT, as is typically seen after cataract surgery with the use of viscoelastic.

Here we see a listing of perioperative complications that occurred with an incidence of one percent or more. Most of these complications are typical of large incision cataract surgery, although some cases of Descemet's detachment may have been related to the large profile of the IMT.

Eight eyes developed posterior capsular pacification. However, this was not visually significant.

A surgical capsulotomy has been performed in two IMT implanted eyes, one in a patient who had completed the phase one trial of the IMT, and the other in a patient who completed 24 months of follow up in the current study and had exited the trial.

Capsulotomy through the clear carrier plate of the IMT has been successfully performed in animal models.

Postoperative adverse events occurring in less than five percent of eyes as well were typical of those associated with large incision cataract surgery, with the exception of corneal edema, device failure, and inflammatory membranes on the IMT.

This slide lists the adverse events with a cumulative incidence of five percent or more. Iris transillumination defect result from surgical manipulation during phacoemulsification or IMT insertion.

Inflammatory precipitants like this appeared in 24.8 percent of eyes during the early postoperative period. They respond to dilation and steroid treatment.

We believe they are due to contact between the iris and the IMT. So we recommend dilation for three months after implantation.

The eight IMT removals consist of two device failures, four explants in subjects who were dissatisfied with the outcome, and two cases of corneal decompensation.

Liquid condensed in two IMTs

postoperatively. Examination of the explanted devices revealed cracks in the lateral wall of the telescope. We concluded that these failures were due to improper handling of the IMT and/or problems with the manufacturing process.

After additional physician training and modification of the manufacturing process, the problems did not recur.

Four subjects were dissatisfied with the outcome and requested IOL removal, with standard IOL implantation. Three of these subjects complained of glare and bright light, and the other noted haze, loss of peripheral vision in the implanted eye, and loss of depth perception.

Two IMTs were removed because of corneal decompensation. In both of these cases the surgeon encountered positive vitreous pressure, iris prolapse, and shallowing of the anterior chamber during surgery.

In one of the cases, one haptic of the IMT was placed in the capsular bag and the other in the ciliary sulcus. In both cases uneventful corneal transplantation and IOL exchange were performed.

As would be anticipated in an elderly population, a number of major nonocular adverse events were reported. We considered the possibility that

falls and fractures might be related to the IMT.

Here are the descriptive details of the falls and the assessment of the investigators who believe that the accidents were unrelated to the IMT.

In addition the rate of falls in elderly individuals has been reported to be approximately four percent a year for those with normal vision, and 11 percent a year for those with low vision.

The observed rate of falls in the experimental cohort with IMT was two percent per year, half of that reported in patients with normal vision, and less than 20 percent of that reported in elderly patients with low vision.

This leads us to believe that the IMT does not contribute to accidental falls in the relevant patient population.

Let us now discuss endothelial cell density.

A standardized protocol and a central reading center was utilized to analyze endothelial cell morphology after implantation of the IMT.

This particular population presented the unique challenges of poor fixation because of central scotomita preoperatively, and light reflection from the anterior surface of the IMT postoperatively.

There is a significant amount of variability in endothelial cell evaluation even under the best of conditions. The best published case in which a single photographer imaged his own eye utilizing a single reader at a single center had a standard deviation of two percent.

From multicenter studies, precision of measurement varies from eight to 10 percent, even with a single reader.

Here's a set of specular images of a study patient, a 79-year-old male who was pseudophakic in the fellow eye.

The first group of analyses that I will now present were based on the cohort of eyes in the PMA submission of September 2005. All modeling analyses are based on the complete 24-month safety data submitted to FDA in April 2006.

This scatter plot of mean endothelial cell density over time shows that the greatest reduction in endothelial cell density occurs between baseline and three months.

This would be anticipated given the incision size and configuration of the IMT.

After three months the change in endothelial cell density between visits decreases

substantially.

Here we see the mean percentage change from baseline. Again, the greatest percentage loss of endothelial cells occurs between baseline and three months.

An informative comparison to the IMT implanted eyes is provided by the cohort of 36 pseudophakic fellow eyes that had undergone cataract surgery before enrollment in the IMT study.

As you can see there is a wide distribution of endothelial cell densities for this pseudophakic cohort that overlaps the distribution of endothelial cell density in the IMT-implanted fellow eyes of these same subjects.

We observed a 9.5 percent loss of cells from three to 24 months in the IMT-implanted eyes.

Interestingly, the mean endothelial cell density in this population approximated that in the pseudophakic fellow eyes shown in blue.

There was a 2.2 percent loss in the unoperated fellow eyes. Thirteen of the phakic fellow eyes went on to have standard cataract surgery during the study, and the average acute cell loss for this small group was approximately 16 percent.

This slide displays the interval changes

for the three cohorts of eyes, confirming that they were remarkably similar for IMT and traditional IOL implanted fellow eyes.

The variation in endothelial cell density is, however, greater in the IMT eyes.

First we ask, how does the loss in endothelial cell density following IMT implantation compare to published data on conventional cataract surgery?

Interestingly, the published literature reports endothelial cell loss that is not substantially different from that seen with the IMT. This is true even with recent reports of modern small incision surgery.

Since a reduction of endothelial cell density following implantation of the IMT is somewhat greater than the endothelial cell density reduction following standard cataract surgery, we set out next to identify factors that contributed to the acute and overall endothelial cell loss in the IMT implanted eyes.

We used univariate and multivariate analyses, considering the candidate predictive factors shown on this slide.

Day one corneal edema and surgeon

specialty were significantly associated with the change in endothelial cell density at three months.

We applied a similar statistical treatment to identify factors that were associated with the total change in endothelial cell density.

Day one corneal edema and surgeon subspecialty were again associated with the change in endothelial cell density.

There also tended to be a greater endothelial cell loss when surgeons were performing their first cases.

Here we see that the endothelial cell loss was less after implantation in the hands of cornea trained subspecialists, suggesting that training and experience with anterior segment procedures can reduce the amount of endothelial cell loss.

Interestingly, there was a demonstrable learning curve for non-cornea trained surgeons on the right. While cornea-trained surgeons, shown on the left, attained an endothelial cell loss that was similar to that associated with cataract surgery even for their first IMT cases.

We believe that appropriately trained surgeons can implant the IMT with endothelial cell loss similar to that reported for modern cataract

surgery.

Anterior chamber depth had a linear effect on the percentage change in endothelial cell density when considering the first three cases performed by each surgeon, but no effect thereafter.

It should be noted, however, that the predictive power of anterior chamber depth was poor. With only about five percent of endothelial cell density variance at three months, and seven percent of variance at 24 months, explained by differences in anterior chamber depth.

The data indicate that other factors such as vitreous pressure and training have a greater influence on postoperative endothelial cell density that anterior chamber depth.

We believe that surgeon training is critical, and to this end have described an extensive training program in the PMA. Meticulous attention must be paid to surgical detail to avoid iris prolapse and flat anterior chambers.

We advocate the selection of patients with higher endothelial cell densities and greater anterior chamber depths for each surgeon's initial cases.

After identifying the significant contributors to endothelial cell loss and the

mitigators for those contributors, we asked whether the rate of endothelial cell loss decreases with time.

Change in endothelial cell density over time between visits, that is the interval change, is shown in this slide. As you can see there is a decrease in percentage change from three to six months; six to nine; and nine to 12, as would be expected.

However, a two percent gain in endothelial cell density was reported between 12 and 18 months. And this gain in endothelial cell density mathematically resulted in a larger than anticipated decrease from 18 to 24 months.

Interestingly this two percent gain was observed in implanted eyes and fellow eyes, so we know that this is within the variability of the measurement.

In fact we think that this is attributable to images rated as fair or poor at the 18-month visit.

For this reason we have also displayed the change from 12 to 24 months, which was -2.3 percent, as shown on this slide, which depicts annualized percentage changes in endothelial cell density from intervals ending at 24 months.

Clearly the rate of loss continues to

decrease during the follow-up period of the study. This is consistent with acute surgery-related endothelial damage followed by endothelial cell migration and then return to a steady state rate of attrition.

The endothelial cell density at three months is not predictive of the rate of loss at later time points.

We are all concerned about the rate of endothelial cell loss that will occur more than two years after IMT implantation. To answer this question we constructed a piecewise regression model assuming a break or change at three months and nine months after IMT implantation.

This model is consistent with the known pathophysiology of endothelial cell loss after cataract extraction which includes acute cell loss at the time of surgery; a period of endothelial cell migration; and a subsequent long term loss that is seen in the aging population.

Here are the projections based on initial endothelial cell densities of 1,600, 2,000, and 2,500 cells per millimeter square.

Corneal decompensation occurs at about 500 cells per millimeter square, so it is clear that

proper selection criteria can provide a reasonable assurance of a clear cornea for the lifetime of this elderly population with severe debilitating visual loss.

How can the endothelium be protected? We recommend that a minimum endothelial cell density based on age and life expectancy be used as a selection criteria. Patients with higher endothelial cell density and a deeper anterior chamber should probably be selected for each surgeon's initial cases, and a comprehensive surgeon-training program should be implemented.

Ultimately we must balance the risk fo endothelial cell loss with a significant improvement in vision and quality of life that is provided by the IMT. Ninety percent of the study population met ICD-9 criteria for severe and profound visual loss at their preoperative visit.

Two years after IMT implantation, only 45 percent of the population remained in this category. This is a remarkable result for a disease with no existing cure.

The data presented in this application also show a clear improvement in visual function using the validated VFQ-25 instrument, confirming that the

measured objective for improvement in acuity coupled with an appropriate training program translates into a functional improvement in activities of daily life.

The significance of this result is highlighted by the report of Brown and colleagues, who found using utility measurements that patients with age-related macular degeneration would give up half of their remaining years of life for normal vision.

The data show that endothelial cell loss related to the IMT is acute, and not substantially different from that seen in this population following traditional cataract surgery with IOL implantation.

Additional training can minimize endothelial damage.

In summary, the implantable miniature telescope is associated with a defined risk that is not substantially different from that of routine modern cataract surgery.

This risk is manageable by training, appropriate selection of subjects, informed consent, and a multidisciplinary approach, including postoperative visual rehabilitation.

The IMT provides a substantial improvement in visual function for an underserved population with limited treatment options.

This is a painting that is the work of Janet Grant whom you heard from this morning. She spoke about her life changes after implantation of the IMT. We believe the results of this clinical trial justify approval of this device so that it will be available to physicians and patients in this country.

Thank you for your attention.

DR. MATHERS: Does that conclude the presentation from the sponsor?

Okay. We now have approximately 15 minutes for the panel to ask the sponsors questions regarding their presentation.

PANEL QUESTIONS FOR THE SPONSOR

DR. MATHERS: Keep in mind that you may also call back later during this meeting these sponsors to ask them further questions later.

These are primarily for clarification. Do we have someone that would like to ask the panel?

DR. GRIMMETT: Michael Grimmett. I have a couple of questions.

First, just a basic one to Dr. Lane regarding the implantation. Are these fairly stiff haptics, more so than a traditional IOL? I noted in the study that maybe three or four percent weren't in the bag but ended up in the sulcus. Are they hard to

bend?

DR. LANE: The area at the haptic optic junction is indeed stiffer than what you would expect from a traditional multipiece or even a single piece intraocular lens, so yes, they are stiffer.

And that's really the reason for the request for the larger capsulorhexis size, so that implantation of the trailing haptic is a lot easier with that large capsulorhexis.

DR. GRIMMETT: If you could stay there for a minute, I have four questions on the ultrasound slide. Thanks.

The measurement on the slide was 2.54. It looked like that was from the center of the optic to the cornea, or was that a peripheral distance measurement, the peripheral optic endothelial distance?

DR. LANE: I believe that was taken from the center of the IMT disc to the endothelial surface.

DR. GRIMMETT: Do you happen to know the peripheral optic endothelial distance?

DR. LANE: I don't. 2.18 I am told.

DR. GRIMMETT: 2.18? Okay. There were seven eyes I believe in your slide. Do you happen to know the mean anterior chamber depth in those seven

eyes, and what the range was? 3.19 is the mean? Thank you.

At Kellogg I believe there were 12 eyes that were implanted. This group of seven represents a little over half.

Was there a reason that the other eyes were excluded to your knowledge, or why they weren't there?

DR. LANE: I think it had to do with the availability of the instrumentation that was there. I think that was a relatively new instrument that they got during the study.

So I'm not sure, Alan, do you know why?

MS. THORNTON: I'm sorry, Dr. Sugar, could you please come to a microphone?

DR. SUGAR: I'm Alan Sugar, professor of Ophthalmology at the University of Michigan, and I'm a paid consultant to Vision Care Technologies.

The ultrasound biometric scope was purchased sometime during the middle of this study, and this was a convenience sample; it was not a selected sample.

DR. GRIMMETT: Thank you, Dr. Sugar. That concludes my questions at this time.

DR. MATHERS: The chair recognizes Dr.

Sunness.

DR. SUNNESS: I have really two questions.

The first is, you haven't presented any data in terms of the visual acuity of the fellow eye and how that changed over time.

Is that data available?

DR. GORDON: Judy Gordon. That data was not included in the PMA, but those measurements were made.

DR. SUNNESS: And a related question is, how would you try to separate out the effects of the low vision training versus the effect of the IMT itself?

DR. BULLIMORE: This is Mark Bullimore, and since it's my first time talking I declare that I have no financial interest in Vision Care but my travel and expenses to be here today have been paid by Vision Care.

That's a challenge, and one of my responses to some of the questions previously from the FDA about why wasn't the training program more rigorous, my initial response to that was, well, if it was more rigorous how could you tell what was the training program and what was the device?

I tend to look at a couple of things. One

is, in the patients, where you see a clear improvement in visual acuity, those who've gained at least two lines of visual acuity, you see the improvement in the VFQ scores.

In the patients who didn't enjoy that same improvement in visual acuity we don't see such a big change.

Also the subscales on the VFQ-25 that do change seem to reflect what commonsense or clinical wisdom would predict. Those really relate to distance vision, the vision and some of the social functioning questions; whereas the ones that you wouldn't expect to change, like ocular pain, peripheral vision, went in the opposite direction, and general health.

So that's the way I interpret it. I think it's a challenge, and I think the sponsor finds themselves in a difficult position of trying to find the right training program.

We have, in recommending labeling, included a statement that like any optical device the benefits of the IMT really can be maximized by the accompanying program of rehabilitation.

But I'd be interested to hear the panel's thoughts on how much or how little would be advisable in that regard.

DR. MATHERS: Dr. Weiss?

DR. WEISS: I wanted to follow up on a question by Dr. Graham that you had mentioned. There were 14 patients with hyphema, which was almost seven percent. Was there a particular reason that the patients with this device were getting anterior chamber blood?

And as a follow up of that, my concern is the comment made about the stiffness of the haptic. I noted that two patients had cyclodialysis, and these patients did not do well, and that's not a typical finding in current cataract surgery.

Would this be perhaps associated with a sulcus placement of a stiff haptic which could result in bleeding and this complication?

DR. LANE: Well, I think that the hyphema is really a reflection of the large incision. You have a large, you have a 12-millimeter incision that's sclerly based. It's really not clear corneal. And a lot of the blood coming from this was coming from the wound leading to the hyphema, which is clearly from the literature also a risk factor in a large incision non-clear corneal type incision.

With regard to the stiff haptics and the possibility of creating a cyclodialysis cleft or a

cyclodialysis - I think that is certainly possible.

I think that the majority of these cases in which there were problems were complicated by other things going on in the surgery such as shallow anterior chambers, and trying to manipulate a very large lens with positive pressure with less space, becomes very difficult. And exact placement of the haptics becomes very difficult.

And I think in some cases perhaps the best judgment wasn't used in placing the lenses at that time due to those kinds of complications in an attempt to just get the lens in. There were problems related to properly positioning the lens within the capsular bag.

However, there have been cases that we did have in which there was one haptic in the bag, one haptic out of the bag, which did well, without any complications. So I don't think that the personal feeling is that the stiffness of the haptics is really more of a challenge of placing the lens than it is a postoperative external pressure device creating difficulties within the angle or within the bag itself if you are able to get it in the bag.

The stiffness is in terms of bending the haptic, not in terms of the external forces that are

in its expanded normal resting state.

DR. WEISS: Another, just a final question not related is, two patients who were having visually significant PCO had needling of the capsule instead of YAG capsulotomy. I know this data wasn't presented during the sponsor's presentation.

But if recommendation is made afterwards of the type of YAG capsulotomy one would want to perform on such patients, why did the sponsors, investigators, not choose to do that during the study?

DR. LANE: If there is a capsulotomy that is going to be attempted with the YAG laser, there has to be adequate pupillary dilation to be able to get out to the clear carrier portion of the IMT.

And I know at least in one of the cases that wasn't possible. So if you can't get out, and you can't shoot the laser through the optical device itself, you're not left with any alternatives to YAG - or to capsulotomy with a YAG laser, and was the reason at least for the one needling.

And I'm not sure of the second.

DR. WEISS: I would agree with you. But as I recall in the information to the physician here, there is a recommendation with the YAG capsulotomy if there are adhesions to dissect this. And I believe

they said, dissect it with a laser, and I wanted to find out how you do that.

DR. LANE: To my knowledge that hasn't been attempted. I mean the most use of the laser is on a patient I had in which pigment was present on the surface of the lens. And I used the YAG laser on a very low setting to essentially dust off the pigment on the surface of the lens.

But to truly dissect the synechia that might be present from the iris to the base of the cylinder, or to the carrier plate itself I think would be quite difficult.

DR. WEISS: This is on page 57 amendment 6.4, posterior capsular opacification; ensure there are no adhesions between the pupillary margin of the iris and the telescope apparatus. If adhesions are present carefully dissect the adhesions with a laser.

So I would presume that that might not be advised.

DR. LANE: Well, I think to a certain extent, Dr. Weiss, it would depend on the extent of the adhesions. A single adhesion that might be causing like a single synechia may be able to be broken by a YAG laser. But obviously if there's extensive 360 degree synechia I think that would be

very difficult if not impossible.

DR. GORDON: I'll just add that all of the labeling that you see is proposed draft labeling, and of course will be revised based on recommendations by FDA and by the panel.

Thank you.

DR. MATHERS: I believe Dr. Palta had a question.

DR. PALTA: Yes, I had two questions.

The first one was just to make sure that I understand the first line on page 25 correctly.

That one seems to be limited to people who had extreme difficulty or had abandoned their activity at baseline, right? And then it shows the percent at follow up who were in different categories. Is that correct, I understand?

So that for example 75 percent - no, I'm sorry, 85 percent were still not able to read newspapers, is that correct?

MS. THORNTON: Judy, your microphone needs to be turned on.

DR. GORDON: Oh, I apologize. We found the slide. We have a one slide per page copy here.

DR. PALTA: So you might have to divide by two maybe. So I just wanted to make sure I

understood correctly that 59 plus 26 percent had no change in being able to read a newspaper?

DR. BRESSLER: That's absolutely correct. And when you administer the VFQ, even in a mildly impaired population, this is the most difficult question or the most difficult task on the VFQ. It's the one where people's scores start to drop first, and it's the one that's most difficult to move.

For your reference, you recall that the entry criterion for the study was 20/80 to 20/800. So even if you had a patient who had 20/80 acuity, receiving, say, a 2.2X telescope, even after the implantation they're going to be about 20/40, and a patient with 20/40 would still probably report moderate and maybe even extreme difficulty with normal newspaper print; it's a very difficult task.

And we only had 10 percent of our total cohort in that first group, so even with the magnification produced by the IMT, we weren't surprised that for this particular very difficult task that the patients were coming up a lot shorter than what they might have desired.

DR. PALTA: My other question is more statistical.

You were referring to a final model. Was

that the piecewise linear mixed effect model? And related to that question, you had sent some material where they were making some exponential models, and you didn't attempt those exponential models?

DR. GORDON: This is Judy Gordon.

The initial model describes, and when we examined it in multivariate and univariate analyses, there were some modeling done, that that was not the piecewise; it was an early effort to identify the factors that contributed to the initial cell loss, significant cell loss that we saw at three months.

Later, as we moved beyond that, the modeling exercises included the piecewise, the three piece, piecewise regression model. So that first reference in the slide is not to that. The only slide that shows a piecewise regression was the one with the curves.

DR. PALTA: Well, you said something about how you added predictive factors to the final model, which probably was the three-piece model where you were looking at some of the predictors of the loss.

DR. GORDON: Well, certainly I think the curve of the loss and the changes over time suggested that there was a change in rate of endothelial cell loss such that the initial loss at three months

represented the first rate, and then the slowing rate of loss at nine months suggested the second rate modeled in the piecewise regression model.

Dr. Edelhauser, I don't know if you have something to add?

DR. EDELHAUSER: I'm Hank Edelhauser. I have no financial interest in Vision Care, but the sponsor has paid for my travel and expenses.

All these models to model the corneal endothelium I think are based almost on - this is a three-pronged approach or three-piece model. But in modeling it's very difficult to take into consideration the peripheral endothelial cell densities.

And when you look oat the peripheral endothelial cell densities, if you move off-center by two millimeters, there is a high percent increase in endothelial cell density.

And if you move off-center four millimeters, there's a 10 percent increase in peripheral endothelial cell density.

And then if you get out toward Schwalbe's line, there could be as high as 20 to 30 percent.

And so this modeling has not taken into consideration that increased peripheral endothelial

cell density.

DR. MATHERS: Okay, chair recognizes Dr. Heuer.

DR. HEUER: At least among the cohort with better preoperative vision, was there any attempt to assess to what degree removing the cataract alone might have contributed to the vision improvement?

DR. BULLIMORE: That's a very good question, and one of the very first questions I asked when I was presented with the data. How much of the vision improvement is due to the cataract extraction?

I really come back to two things. One is the judgment of the treating physician, because that was an entry requirement that the patients really not have any visually significant cataract. And if you look at, particularly for the 2.2X telescope, improvement of vision that was gained with the IMT closely matched that which was obtained with the external telescope.

So preoperatively, before the cataract was removed, or before the lens was removed, they were achieving pretty much the same visual acuity with the external telescope that they ultimately got at 12 months with the IMT.

DR. MATHERS: Dr. Huang.

DR. HUANG: Andrew Huang. I have two questions.

The first question is regarding safety. In the initial enrollment there were seven patients excluded from implantation due to the posterior capsule rupture, and in the final tabulation they were indicating 10 patients with posterior capsule rupture.

So my question is, was there any patient after the implantation had a posterior capsule rupture and lead to these incidents?

DR. GORDON: This is Judy Gordon. We'll have to look that up to see how the additional three were categorized, and we will answer your question after we have a chance to look it up in our data.

DR. HUANG: Thank you. And second question is regarding the efficacy. In the VFQ-25 subscales, it seemed to me very interesting that this device is intended to improve the patient's distance vision. However the patient’s indication that most of them indicate there is significant improvement of the near vision.

Is there any explanation or any from the patient's perspective?

DR. BULLIMORE: Yeah, just to clarify, this is not a multifocal device. And essentially the

patient will be functioning like any other presbyopic patient wherein bifocals or reading glasses as needed.

The patients do enjoy benefit both in terms of their distance vision and near. So to us it's not unexpected that they enjoy improvements in the VFQ subscales both in terms of their distance vision and their near vision.

DR. HUANG: Was this measured binocularly? Or is this a uniocular measurement of the near vision in terms of the questioning administration?

DR. BULLIMORE: In terms of the VFQ, the VFQ was presented as recommended by its designers, and it concerns the patients' habitual vision, binocular vision, and includes qualifiers about - with appropriate contact lenses, spectacles and such like.

So the questions were not directed in a way that the patient was asked about, with your treated eye. It was just administered in the typical form regarding their habitual visual function.

DR. MATHERS: Dr. Bressler.

DR. BRESSLER: Neil Bressler. I had a few methodology or design questions, so please choose whoever can answer it.

The first was, to get enrolled they had to have no active CNV on fluorescein angiography, and I

was just wondering what the definition of no active CNV was. Was that specified more than that, or was a gestalt interpretation of that phrase?

DR. HEIER: They had to have no signs of activity, meaning no signs of active neovascularization or bleeding within the past six months.

DR. BRESSLER: So did active mean no fluorescein leakage?

DR. HEIER: It did.

DR. BRESSLER: Okay, no fluorescein leakage, okay.

The next one was, I was curious on the eleven eyes where you did not successfully implant the telescope, how much vision outcome do you have on those? Were they followed through one year? And what were those results if you have them?

DR. GORDON: We can get a listing of that for you and answer in more detail. But we followed those patients for periods of at least - as long as those patients would be willing to come back. And there was no loss of vision from their baseline preoperative vision.

DR. BRESSLER: In all 11?

DR. GORDON: Yes.

DR. BRESSLER: Okay. And you went from 203 or something, 206 to 193, and what did you do with the 12-month outcomes for the people, those 13 people that weren't followed at 12 months? Did you use last observation carried forward? Did you just use the observed data?

DR. GORDON: We used observed data in all analyses, which I'd just add a comment, which is actually very typically done in a device trial. And I think supported by the fact that we had over 90 percent accountability both at 12 and at 24 months. So the contribution of those eyes, I think, has less impact, so an LOC I think would not be requested or required.

DR. BRESSLER: And do you have the information on those 13 eyes, what their last vision was before they were not followed again?

DR. GORDON: Yes, the slide that we showed showing loss of lines of acuity was for last available. That reflects the last available visual acuity, meaning if they came in with requests for an explant or for whatever was available, that was included, other than for the explants at baseline I think.

But I will confirm that. I think that was

from -

DR. BRESSLER: Which slide was that, I'm sorry, on the vision outcome? You can check that. I just had two or three other quick design - no, I can come back to them later.

DR. MATHERS: Why don't we come back to them later.

DR. BRESSLER: Okay, that's fine.

DR. MATHERS: We will have an opportunity to do that.

Okay, we're going to move now to the FDA presentation. And the first FDA presenter is Dr. Calogero.

MS. THORNTON: Will the sponsor please return to their seats.

DR. MATHERS: Yes, Dr. Ferris.

DR. FERRIS: So if there is a minute, I at least for one am confused by the issue of these being clear lenses, and the eligibility criteria saying there has to be evidence of cataract.

And to me this is really a critical feature to understanding the -- with no control group to understanding the effect of the device. So if there could be at least a brief discussion of that.

MS. THORNTON: We will allow the answer to

come forward until the point that FDA is ready. If FDA is ready now, then we'd like to defer the answer to your question at a later time.

DR. MATHERS: We will come back to it.

MS. THORNTON: We will come back to it. I know you won't forget it.

(Laughter)

DR. MATHERS: We're going to come back to further questions.

So we will begin now with the FDA presentation.

FDA PRESENTATION

MR. CALOGERO: Okay. My name is Don Calogero. I'm team leader for PMA, P050034.

As you already know this PMA is for the implantable miniature telescope, or the IMT.

It was originally submitted to FDA as a modular PMA, and as you know, it's for patients with central vision impairment due to macular degeneration.

There are two models proposed in this PMA, a model 2.2, which corresponds to 2.2X magnification, and a model 3.0X, which corresponds according to the PMA to 2.7X magnification, but during these presentations it was identified as 2.8 magnification, so it's not clear what the true magnification is.

On the left hand side of the slide you'll see a diagram of this device. It has an overall diameter of 13.5 millimeters, and an overall depth of 4.36 millimeters. Of that 4.36 millimeters, 1.84 millimeters is anterior to the haptic plane, and 2.12 millimeters is posterior to the haptic plane, with the haptic plate being .4 millimeters thick.

The sponsors indicated that the anterior surface of the telescope protrudes approximately .6 millimeters into the anterior chamber.

Because of the magnification associated with this device, the retinal luminescence is reduced by about .7 log units for the model 2.2X, and approximately .9 log units for the model 3.0, if it turns out to be 2.7 as opposed to 2.8.

In terms of preclinical testing the standard battery was performed for this device and this PMA. Biocompatibility testing adhered to the relevant testing in both the horizontal 10993 and the vertical standard for this type of intraocular implant.

In terms of physical-chemical testing, testing was performed in terms of extraction, hydro lipid stability, exhaustive extraction, photo stability and periphery neodymium YAG testing, and

also the standard battery for sterilization packaging and shelf life.

FDA has no remaining concerns regarding preclinical testing.

I'd like to acknowledge the review team for this PMA. In addition to being the team leader, I also performed the manufacturing review.

Dr. Bernard Lepri performed the clinical review.

The statistical was a team of Drs. T.C. Lu, Yao Huang, Ning Li, and Gene Hilmantel.

Vision science was performed by Dr. Bruce Drum; biocompatibility, Ms. Susanna Jones; microbiology, Ms. Sara Thornton; and epidemiology, Dr. Michele Bonhomme.

At this time Dr. Lepri will come up and present the clinical review.

DR. LEPRI: Good morning, panel members, members of industry, FDA colleagues.

I would first like to present to you a special thanks to Gene Hilmantel, who is my Rosetta stone of biostatistics, and for Bruce Drum, the walking guide to visual science and contributor of the visual science and visual field slides at this presentation.

And a special thanks to the sponsors for their friendliness and cooperativeness throughout this long enduring project.

And I would also like to mention - it sounds like the Academy Awards, doesn't it? -- the beneficial help and cooperation of our statistical team and epidemiological team.

The introductions now being completed, I will now present to you FDA's analyses of the critical clinical outcomes to be used in your deliberations regarding this PMA.

The panel's challenge today will be to define to characteristics of the macular degeneration population that have the potential for the best risk-benefit ratio.

The proposed indication reads: The IMT is indicated for use in adult patients with bilateral stable untreatable moderate to profound central vision impairment due to macular degeneration as determined by fluorescein angiography and cataract in patients who are 55 years of age or older; have a best corrected distance visual acuity ranging from 20/80 to 20/800; have adequate peripheral vision in the nonoperative eye. And demonstrate a minimum five-letter improvement on the ETBRS chart with an external

telescope.

The sponsor conducted a prospective multicenter clinical evaluation of the use of the IMT implant in subjects with bilateral stable untreatable moderate to profound central vision impairment due to dry age-related macular degeneration who also have cataracts.

The study was conducted in the United States under an improved IDE. There were a total of 218 consecutive patients enrolled and 206 patients were implanted and evaluated at 28 clinical sites followed over a 24-month period.

At the time of database closure 194 eyes had reached the 12-month follow up; 180 eyes had reach the 18-month follow up; and 148 eyes had reached the 24-month interval.

The primary effectiveness endpoint is defined as an improvement of greater than or equal to two lines of either best corrected distance visual acuity or best corrected near visual acuity in 50 percent of the eyes at the 12-month postoperative interval.

The secondary measurement of procedure success was the performance on the quality of life surveys, the VFQ and the ADL.

The safety endpoints are as follows. The endothelial cell loss was to be a mean percent of ECD loss of less than or equal to 17 percent at one year postop. This was the primary safety endpoint.

Preservation of best corrected visual acuity was to be, for example, no more than 10 percent of implanted eyes were to experience a loss of more than two lines of either near or distance BCVA without a corresponding improvement, a gain of two lines or more, in BCVA, a gain of two or more lines of near-BCVA in eyes with loss of more than two lines of distance BCVA, and vice versa.

Next. Key study outcomes will be discussed in this presentation so that the panel will be able to make recommendations regarding the safety of the IMT with respect to the minimum preoperative endothelial cell density of prospective IMT patients; the minimum anterior chamber depth; and subsequently, the relationship of preoperative endothelial cell density levels with respect to minimum age qualifications for selection.

At one year postoperative IMT implanted eyes demonstrated a 25.3 percent mean decrease in endothelial cell densities.

At two years this mean rate of loss rose

to 28.2 percent.

Also at two years postoperative, we can see that 12.5 percent of implanted IMT eyes demonstrated an endothelial cell density count of less than 1,000 cells per millimeter squared.

For the 10 percent of eyes with the greatest loss, the 90th percentile, there was a 60 percent loss of ECD for IMT implanted eyes, as compared to 12.5 percent for fellow eyes.

This slide presents the proportion of eyes with ECD losses greater than 20 percent over time for IMT implanted eyes in comparison to the fellow eyes. At three months we see that 40 percent of the eyes treated with the IMT had a loss of greater than 20 percent; at 12 and 18 months 50 percent; and at two years 60 percent.

Across all time periods the fellow eyes demonstrate a relatively constant level of ECD counts.

Many factors have been identified as contributing to the endothelial density outcomes of this study. The panel should take into consideration in their deliberations that there was no morphometric data presented by the sponsor. The issue of surgical order, anterior chamber depths of less than 3 millimeters, as well as surgeon specialty when making

recommendations for defining the indications and labeling for the IMT if approved.

In addition to these factors the panel should also take into account that according to the United States life tables tabulated in 2002 the life expectancy for a person currently 60 years old is 22 additional years, and for a person 90 years of age a potential additional lifespan of five more years is expected.

One can easily see that age is an important consideration in patient selection.

FDA requested an analysis of the number of eyes that would progress to an endothelial cell density of less than or equal to 1,000 cells per millimeter squared. Since the potential for corneal edema occurs at endothelial cell densities of less than or equal to 800 cells. This next slide presents the results of that analysis.

These data were generated by FDA statisticians, and they will be presenting you with the details of their analyses following the clinical presentation.

We can see that at two years 11.1 percent of eyes are projected to have a cell density of less than 1,000; at three years 17.6 percent; and at four

years 22.7 percent.

This chart clearly shows that the number of IMT eyes whose ECD falls to 1,000 or less increases with each advancing postop time interval out to four years as compared to fellow eyes.

The next item for discussion is anterior chamber depth.

Anterior chamber depth is related to the ECD loss sustained by IMT patients. The length of the IMT, 4.4 millimeters, in conjunction with shallower anterior chambers, may induce endothelial cell loss by the increased potential for surgical trauma, and by the proximity of the IMT to the endothelium post implantation.

The sponsor reported an anterior chamber depth has a major impact on ECD loss rates in the first six months postop. While these related losses do not appear to contribute to the chronic rate of loss, they are permanent, and thus have the potential to impact corneal integrity and function.

The next slide, the slide that's currently up there, will present data related to the various strata of anterior chamber depths represented in the IMT clinical trial as analyzed by FDA.

Go back to the previous slide. Eyes with

anterior chamber depths of less than three millimeters have the greatest losses at all time periods, and especially at 24 months where approximately one-third of endothelial cell density has been lost.

Anterior chamber depths ranging from greater than three millimeters to 3.5 millimeters showed clinically significant less ECD loss than those with anterior chamber depths of three millimeters or less.

These losses range anywhere from 2.8 percent to 6.3 percent less than anterior chamber depths of less than or equal to three millimeters.

Likewise eyes with anterior chamber depths of greater than 3.5 millimeters showed clinically significantly less ECD loss than eyes with anterior chamber depths of three millimeters or less.

These losses range from 4.7 percent to 7.7 percent less than losses of eyes with anterior chamber depths of 3.0 or less.

And it is also noteworthy that both of the patients who experience corneal decompensation in subsequent transplant had anterior chamber depths of less than three millimeters.

The IMT is designed for a two millimeter corneal endothelial clearance. The study selection

criteria utilized a minimum anterior chamber depth of 2.5 millimeters.

No substudies were performed or data presented in the PMA to establish the suitability of the proposed minimum anterior chamber depth for the established minimum clearance of 2.0 millimeters.

Haptic placement: the average anterior chamber depth represented in the PMA study cohort was 3.15 millimeters with a standard deviation of plus or minus 0.37.

It has been published in the IMT literature that placing the IMT in the sulcus as opposed to completely in the bag moves the device anteriorly and increases the risk of corneal touch.

Taking the mean anterior depth represented in this study, the percentage of sulcus-placed devices range from approximately 2.5 to 4 percent, and the rates of surgical and chronic loss into account should be considered also.

The panel has one more reason to carefully weigh the importance of anterior chamber depth.

During the course of the clinical trial one eye was reported to have PCO at 18 months, and two eyes had visually significant PCO at 24 months.

The sponsor claims that they utilized

specific design objectives to minimize the occurrence of posterior capsular opacification, and the primary elements of these design objectives included the biocompatibility of the material used, the geometry of the device, and its alignment with the capsular bag.

YAG capsulotomies for visually significant PCO were not performed during the IMT clinical trial. However, due to two cases of visually significant PCO, the sponsor utilized the needling procedure to address the events.

YAG capsulotomies, as I said, were not performed, because the sponsor has identified that these lenses contained within the IMT telescope can be damaged by the laser.

The sponsor has proposed labeling to provide instruction to the physician regarding the performance of a YAG capsulotomy through the periphery of the telescope, as well as recommending the needling procedure.

YAG capsulotomy was successfully performed in eight rabbit eyes implanted with the IMT, and the results of this study were reported in the Journal of Cataract and Refractive Surgery in 2003.

There are in fact potential problems with YAG procedures with the IMT. Performing a YAG

capsulotomy as recommended by the sponsor can only be done around the periphery of the IMT. This would require significant increases in the number of bursts of energy required to achieve the capsulotomy, and increase the total amount of energy delivered to the eye, subsequently increasing the risk of retinal detachment.

And finally, because the apposition of the IMT against the posterior aspect of the capsular bag is so important in its implantation, it is unknown what effect a YAG will have on this positioning.

The sponsor has not provided any information regarding this issue.

Clinical effectiveness was evaluated by visual acuity outcomes as well as the results of quality of life questionnaires. The panel will be asked to evaluate various data on clinical effectiveness based on improvement of both best corrected distance visual acuity, and best corrected near visual acuity, as well as improvements in quality of life measures.

In the discussion of the effectiveness of outcomes of the IMT it is important to establish the various categories of vision loss represented in the study population.

These are accepted categories of definitions of low vision.

Visual impairment is defined as a best corrected vision of less than or equal to 20/40, but not better than 20/200.

Legal blindness is defined as the best corrected distance visual acuity of less than or equal to 20/200, and a visual field diameter of less than 10 degrees.

And low vision in general is defined as a best corrected distance visual acuity of less than 20/60 in the better eye.

The mean preoperative visual acuity data for both distance and near for the IMT clinical trial indicates that most of the subjects in this clinical trial were categorized as legally blind. The mean preop best corrected distance visual acuity was 20/312, and the mean preop best corrected near visual acuity at eight inches was 20/315 and at 16 inches was 20/262.

The implantation profile for this device is that 115 eyes were implanted with the 2.2X telescope and 91 eyes were implanted with the 3.0X telescope.

As one can see from this slide, explain

correction improvement in vision, there was a large proportion of eyes reported to have had significant improvements in acuity. But can patients actually see and do more?

In light of significant fluctuations in repeated measures of acuity in macular degeneration patients, the panel will be asked to decide if the reported proportions of acuity improvements greater than or equal to two lines preoperatively provides sufficient benefit with respect to the safety risks of the IMT.

For IMT implanted eyes, 90.1 percent of implanted eyes are reported to have had an improvement of greater than or equal to two lines in either best corrected distance visual acuity or best corrected near visual acuity at 12 months postop.

For refractive lasers and phakic IOLs a change of greater than or equal to two lines denotes a clinically significant change in visual function. These eyes are not diseased or considered low vision or legally blind.

The panel should weigh the value of evaluating successful outcomes from the IMT with respect to the criterion of improvement in lines of visual acuity only.

This slide presents the reliability of low vision measures as constructed by Russell Woods and Jan Lovie-Kitchin from the Center for Eye Research, School of Optometry, Queensland University of Technology.

This table shows that previously reported repeatability coefficients for young normal subjects are significantly smaller than those found in a study of low vision subjects and uncorrected normal vision subjects.

This is consistent with the repeatability coefficients reported for subjects with moderate ocular disease, and subjects with optically degraded vision.

It is also consistent with the suggestion that the repeatability coefficient increases as the average visual performance of the group reduces as shown in this table.

The data on this chart, taken from the PMA application, indicate that those subjects with severe and profound vision loss, representing the largest proportion of subjects within the cohort, showed greater than three lines of improvement in visual acuity.

Technically, the acuity predicted from the

magnified postoperative retinal image should result in acuity increases of three lines or 0.3 LogMAR units relative to the preoperative acuity at the very least.

The predicted postop acuities for the mean preoperative BCDVA of 20/312 with the 3X IMT having a nominal magnification of 2.7 would be approximately 20/115.

With the 2.2X telescope the predicted postop BCDVA would be approximately 20/142.

The mean BCDVA at 24 months reported by the sponsor was 20/150, and this was for both groups of patients for both telescopes.

This was achieved by 52 percent of the available cohort at that time having greater than approximately three line improvement of best corrected acuity by year two.

The safety and effectiveness for visual acuity are based on unadjusted baseline acuity, and not on acuity predicted from the magnified postoperative retinal image.

Next slide. Back one. The predicted postop acuities for the mean preop best corrected near visual acuity of 315 at eight inches, assuming an average improvement of approximately three lines of acuity, would be 20/105.

At 16 inches the predicted acuity would be 20/87. In actuality, the mean acuities achieved by 24 months postop were 20/190 at the eight inch test distance and 20/157.6 at the 16-inch test distance.

The safety and effectiveness for visual acuity are, as we said, based on unadjusted baseline acuity and not on acuity predicted from the magnified postoperative retinal image.

There are also no data showing how much acuity improved as a result of the cataract removal alone.

Preoperative acuity measurements were not adjusted. If the IMT performs its intended optical function of magnifying the retinal image by either 2.2 or 2.7 times without affecting corneal or retinal function, measured acuity should increase by approximately 3.4 or 4.3 lines respectively.

Now a measured two-line loss is really 5.4 for the 2.2X telescope or 6.3 for the 3X telescope lines from a retinal standpoint, an apparent improvement ranging from less than 1.4 to less than 2.3 lines is really a loss of greater than two lines from a retinal standpoint.

The panel will be asked to determine whether the unadjusted preoperative acuity baseline is

acceptable for evaluation of safety and efficacy of this device, or should adjusted baseline acuities be used as well?

Safety and effectiveness: the panel will be asked to address not only the objective visual acuity data, but the functional safety and effectiveness of the IMT as addressed by the vision rehabilitation program utilized in the clinical trial.

Items five, six, seven, eight and nine of the VFQ-25 address the concerns of independent mobility, reading street signs and names of stores, negotiating steps and curbs, and reading ordinary print in newspapers.

While the entire VFQ-25 assesses visual function by self report, these specific items are strongly related to the areas of visual difficulty for macular degeneration patients.

The sponsor presented the mean scores and mean changes in scores for both the VFQ and ADL questionnaires. FDA requested that the sponsor provide FDA with the frequency analyses for each rating within each category assessed in these questionnaires for both the scores and change in score analyses.

FDA requested this because the mean does

not tell the whole story. The frequency analyses for each rating within each category assessed in the NEI VFQ show that subjects reporting extreme difficulty with the items pertaining to visual function decreased in number by one year postop as seen on the sponsor's slides previously.

Subjects reporting little and moderate levels of difficulty increased at one year, and it is unclear from the data reported in the PMA whether some of the subjects who initially reported extreme difficulty subsequently reported moderate difficulty in the postoperative periods.

Vision Care's rehab program: IMT patients were given written directions, and with assistance from family members, were to practice many demanding tasks such as walking, reading, and associated tasks of daily living.

The program did not utilize any direct performance measures of the pre- and post-implantation skills of the study patients.

Family members directed the home training program, and were responsible for making environmental modifications.

At their scheduled visits optometrists and ophthalmic technicians, many of whom had low vision

training, checked on the progress of the rehabilitation program and provided additional instruction.

The IMT patients were not professionally instructed on safe mobility and navigation in their home environments or work environments if pertaining, and did not have reading instruction by low vision reading instructors.

What is successful rehabilitation? Massot from the Wilmer Eye Institute defines success in low vision rehabilitation as reduction in the level of difficulty in performing a particular task or goal or the reduction in the importance of that task by teaching the patient alternative strategies to achieve the goal.

In other words every vision rehabilitation program requires targets before you start, and these are the aims and goals of that rehabilitation program.

It is individualized, and that explains the lack of a standardized regime on vision rehabilitation in the literature.

Next slide. Numerous studies verified that vision rehabilitation with specific targeted goals, directed by vision rehabilitation specialists, yields a high rate of success that is sustained over

time.

As early as 1944 Langmann, et al, identified that the failure rate decreased from 22 percent to 3 percent. A survey of veterans at the Low Vision Center in Atlanta revealed that after 12 and 24 months at least 85.4 percent of the devices were still in use. And these are external devices; 85.5 percent were found to still be using their optical assistive devices two years later. And 77 percent of 261 cases used optical devices successfully as reported by Van Rens in 1991.

It is known that this improves function. Training is critical to success.

Visual loss and falls: annually 25 percent to 35 percent of older persons fall, and more than 40 percent of these falls result in hospitalization.

Nevitt (phonetic), et al, reported a threefold risk for multiple falls with poor vision, and the Beaver Dam Eye Study reported that for individuals over the age of 60, with acuity of less than 20/25, 11 percent suffered injurious falls every year as compared to only 4.4 percent of those with normal visual acuity.

During the course of the IMT clinical trial, there were eight monocular adverse events.

These occurred after implantation, and consisted of four fractures, one contusion, and other forms of injury related to falls.

These may have been due to some of the effects of magnification in some of these cases. Magnification alters proprioceptive senses and creates a safety issue for the newly implanted IMT patient.

Training by low vision specialists should be a requirement of this device. However, since most physicians will not have direct access to mobility and orientation training specialists, they will need to make referrals to agencies for these services.

State associations for the blind and visually impaired are mandated in every state in addition to other agencies serving the needs of the visually impaired.

The patients who are to practice exercises for learning to suppress central vision in the IMT eye when performing visually demanding tasks such as walking which requires the use of peripheral vision.

The program was directed by the family members and did not utilize any direct performance measures of the subject's ability to voluntarily shift binocular suppression from one eye to the other.

The implantation of the IMT is proposed to

be used both binocularly and monocularly. This presents a significant concern regarding binocular performance. Among these are: noncorrespondence of overlapping fields, forcing binocular rivalry and suppression; severe visual field restriction in the dominant eye, the IMT eye; motion discrepancies in magnified and unmagnified fields; and possible suppression of the entire fellow eye.

The monocular field extends greatly to the temporal aspect, and is curtailed nasally with the superior and inferior fields being somewhat equal.

The binocular field is simply the combination with the two monocular fields which result in an area of overlap that supports stereoscopic binocular vision.

For macular degeneration patients a dense scotoma extends out to about four to five degrees of eccentricity, but the entire peripheral field beyond the central scotoma remains normal.

In this slide we see the subjective field of the IMT implanted eye. However, when the IMT is implanted all visual stimulation is permanently blocked outside the telescopic field of view.

This plot shows the subjective IMT field of about 54 degrees diameter minus the central

scotoma. The outer boundary is similar to the area covered by a conventional Humphrey 24-2 visual field.

In terms of the information from the environment, however, this field covers only 20 to 24 degrees in diameter, depending on the IMT magnification. The effect of central scotoma is decreased proportionally to the amount of the magnification of the telescope as seen in the objective field of this IMT eye.

The monocular field of the fellow eye is, of course, unaffected by the IMT implantation, as you can see there. If an IMT patient were able to optimally use the information to both eyes, the combined field would exclude stereopsis, but would otherwise be equivalent to the fellow eye field with improved central acuity and a reduced central scotoma.

When the IMT eye suppresses the overlapping part of the fellow eye field, however, neither eye receives information about the annular region from 10 to 27 degrees of eccentricity.

Motion is a powerful stimulus for focusing attention. For IMT patients retinal images move proportionally farther and faster in the magnified IMT field in comparison to the fellow eye, only using the peripheral field.

For example object motion, head motion, consensual eye movements, and motion through the environment. Discordant motion information can also cause disorientation, vertigo, and/or motion sickness if both moving images are seen together.

No such symptoms were reported for IMT subjects.

This suggests suppression of either the IMT image or the entire fellow eye image. Vision Care has provided no data regarding this issue.

Since the IMT receives the more prominent motion stimulus, the second possibility seems more likely.

As this slide illustrates, this would leave the IMT patient receiving effective visual input to only the central 20 or 24 degrees of field. The possibility exists that at least some IMT patients could experience this effect without noticing that their visual field is severely constricted.

Risks versus benefits: the discussion of this device warrants careful consideration of the reported improvements in visual acuity with respect to the postoperative risks of ECD loss, potential perceptual adjustment problems, and unknown problems with examination and treatment of an IMT implanted

eye.

Thank you for your attention.

At this time I would like to introduce T.C. Lu and Yao Huang, the consulting statisticians for this PMA. They will now deliver their presentation.

DR. LU: My name is T.C. Lu. I'm a mathematical studies teacher at the division of biostatistics at FDA.

A major concern about this device is the endothelial density loss over time. Our statistical review will focus on the 24-month database.

The 24-month database includes all the records except those of the patients that were lost to follow up; patients who discontinue prior to their 24 month visit were still included in the database. Both IMT and the fellow eye data are used.

This scatter diagrams indicate that the ECD counts over time. The X axis is the time in months, which ranges from zero to 25.

And the Y axis is the ECD counts. The left panel is for the IMT eyes, and the right panel is for the fellow eyes. Each dot represents an observation.

There are four major issues for which we

would like your consideration. The first issue is the mean ECD loss over time. We are looking at the two time periods, one from baseline to three months, and from three months to 24 months.

The second issue is the distribution of ECD loss. In this analysis we compare the percent of IMT eyes with ECD loss to the percent of fellow eyes with ECD loss. Also, we stratify the percent ECD loss into two categories: ECD loss greater than 10 percent; and ECD loss greater than 50 percent.

The third issue relates to the anterior chamber depth, ECD and the surgical order.

The fourth issue is related to estimating how long it will take from the ECD in the IMT eye to reach 1,000 or lower.

I will address the first issue. The ECD percent loss from baseline to three months associated with surgery is 20 percent. And the 95 percent of confidence interval is from 17 percent to 23 percent.

The chronicle of ECD percent loss in terms of yearly average loss is 5.4 percent, and the 95 percent of confidence interval is from 2.0 percent to 8.8 percent.

This graph shows the mean ECD for IMT eyes from baseline to 24 months. The X axis is the time in

months, and the Y axis is the ECD. The mean ECD of IMT eye at the baseline is 24/96.

Let us add the mean ECD for fellow eyes to the previous graph. The color, orange, is for the fellow eyes, and the color blue is for the IMT eyes. The vertical bars represent one standard deviation above and below the mean value.

The mean ECD for fellow eyes at the baseline is 2431.

Let us look at the comparison of IMT eyes and the fellow eyes of ECD loss more than 10 percent at each follow up time. For example, eight months, 59 percent of the IMT eyes versus 5 percent of the fellow eyes that had ECD loss more than 10 percent.

The proportion of patients with ECD loss greater than 10 percent is numerically larger for the IMT eyes than the fellow eyes.

The proportion of patients with at least a 10 percent ECD loss in the IMT eyes ranges from 59 percent at the three months to 76 percent at 24 months.

This slide compares the ECD loss more than 50 percent. In fact none of the fellow eyes had more than 20 percent ECD loss. The proportion of patients with at least a 50 percent ECD loss in the IMT eyes

ranges from 12 percent at three months to 19 percent at 24 months.

We are now looking at the ECD percent change in the IMT eyes. Time is divided into three groups: baseline to three months; three months to 24 months; and the baseline to 24 months.

The ECD percent change for five, 10, 20 and 50 percentiles are provided in this table.

The percents themselves represented a percent of ECD loss corresponding to each percentile of the distribution of ECD.

Half of the IMT eyes had at least 80 percent of the ECD loss from three months to 24 months.

Let's look at this five percent. This indicated that the worst of five percent are IMT eyes had at least 67 percent of ECD loss associated with surgery from baseline to three months.

Let us turn to the third issue: there are two potential clinical factors that may affect ECD loss: ECD, and the surgical orders. The mean standard deviation and the range for ECD are provided.

The mean of ECD in IMT eyes is 3.147 millimeters. The standard deviation is .38 millimeters, and the range is from 2.4 millimeters to

4.74 millimeters.

Surgical order is divided into two groups: less than or equal to three surgical cases; and greater than or equal to four surgical cases.

FDA asked the sponsor to examine the ECD percent change more closely by considering the ECD and surgical order that is known to affect ECD.

The mixed model that includes ECD and the surgical order were recommended by FDA and performed by the sponsor. The sponsor's analysis is summarized as follows: ECD has a linear effect on ECD percent change from baseline to three months, but not from three months to 24 months. Surgical order did not show statistically significant difference.

Now I will turn the podium to Yao Huang. Yao will discuss the fourth issue, how long it will take for the IMT eye to reach an ECD of 1,000 or lower.

Dr. Yao.

DR. YAO: Thank you, T.C.

Good afternoon. I will present the modeling results of the ECD data.

Here are the ECD data for both IMT eyes and fellow eyes. Each connected line is the ECD profile for one subject.

It is noted that at baseline ECD values are similarly distributed for the IMT eyes and fellow eyes.

For the fellow eyes ECD is approximately constant over time. For the IMT eyes there is a large drop in ECD from baseline to three months, and ECD may continue to decrease after three months with a lower rate.

A mixed effect model is fitted to analyze the ECD data, and this is the plot of the mixed effect model. For each group two linear pieces are assumed, baseline to three months as the acute period, and three to 24 months as the chronic period.

It is assumed that IMT eyes and fellow eyes are independent.

The top solid line describes the linear ECD change for the group of fellow eyes.

The bottom solid line is for the group of IMT implanted eyes, and the dotted lines are the 95 percent confidence limits of the estimated ECD means for each group.

And here are the results of the mixed effect model. At baseline, the mean ECD is 2466.89 for both IMT eyes and fellow eyes.

And for the group of IMT eyes ECD dropped

169.81 units per month in the acute period. And ECD continued to decrease with 9.83 units per month during the period from three months to 24 months.

For the group of fellow eyes, the acute ECD loss is 6.59 units per month. However, it is not statistically different than zero.

P values in this table are for testing the null hypothesis of parameter equal to zero.

And based on the mixed-effect model, comparisons of ECD losses have been conducted between three main groups, and between different study periods.

We found that there is a statistically significant difference in acute ECD losses between IMT eyes and fellow eyes.

The chronic ECD loss for IMT eyes is 9.83 per month, and the chronic ECD loss for fellow eyes is 3.03 per month.

The difference between the two loss rates is significant - is statistically significant.

Among the group of IMT eyes, acute ECD loss is significantly different than chronic ECD loss. However, the difference is not significant among fellow eyes.

One question of interest is when ECD would

reach 1,000 or lower if the subjects continued to be observed. Unfortunately, this question cannot be answered based on the available database from baseline to 24 months.

Data extrapolations should not be encouraged because there is no sure knowledge about the ECD pattern outside of the current database.

One consequence is that if the linear trend would not be the same beyond two years, the prediction based on the chronic linear trend may not be reliable.

Nonetheless, in order to provide a rough picture of long term performance of ECD we projected the mean ECD of the study population for four years by assuming the chronic linear trend still holds three or four years.

The pink lines in this plot - in the plots are the projected mean ECD according to the mixed effect model.

The scattered dots are the actual ECD observations from the clinical study. The orange line tells where ECD would be 1,000 or lower.

According to the data from the clinical study for the fellow eyes, all the observations below the orange line of 1,000 came from one subject.

For the IMT eyes, there were 29 subjects with postoperative ECD no more than 1,000. According to the mixed-effect model, by the end of year four the projected mean ECD count for the IMT eyes would be significantly lower than that of the fellow eyes.

This table presents the percentages of eyes with the predicted ECD no more than 1,000 at two, three and four years respectively.

There is a sizeable increase in IMT eyes whose ECD will be 1,000 or lower. For example, at year two, 11.1 percent of the IMT eyes would have ECD no more than 1,000, while .5 percent of the fellow eyes would have such lower ECD.

To further look at the relationship between baseline ECD and long term ECD projection, we stratified the baseline ECD by its quartiles. The baseline ECD of the IMT eyes ranges from 1695 to 3356. The first quartile is 2261, the median is 2513, and the third quartile is 2772.

And here is the prediction of eyes with ECD no more than 1,000 at year two. This table is stratified by baseline ECD quartiles. In the first subgroup 20.4 percent of the IMT eyes would have predicted ECD no more than 1,000 at year two, while 1.9 percent of the fellow eyes would have ECD no more

than 1,000.

In each subgroup more IMT eyes would have ECD no more than 1,000 compared to the fellow eyes.

This is the projection of eyes with ECD no more than 1,000 at year three. The pattern is similar to the prediction at two years. In the first subgroup, 31.5 percent of the IMT eyes would have ECD lower than 1,000, while 3.7 percent of the fellow eyes would have such low ECD.

In other subgroups, the percentages of IMT eyes are nontrivial, while no fellow eyes would have ECD lower than 1,000.

And this is the projection of eyes with ECD less than or equal to 1,000 at year four. In each subgroup the percentage of IMT eyes is not trivial. For those with the best baseline ECD the percentage is as high as 9.3 percent for IMT eyes, with ECD no more than 1,000.

And here are some baseline demographics for the IMT eyes in terms of patient age and anterior chamber depth. Again the table is stratified by baseline ECD quarries.

For the first subgroup the mean age is 76.81, and the mean ECD is 3.10.

There is no statistically significant

difference in either age or ECD across the ECD strata.

And the sponsor agrees that the FDA's two-piecewise model is reasonable, and they provided an additional model using a three-piecewise linear function to fit the ECD data with two breakpoints at three months and nine months.

The model uses the ECD data of the IMT eyes only. Their conclusions, based on the three piecewise models, are consistent with the FDA's model for IMT eyes.

This table presents the results of the sponsor's mixed effect model with two breakpoints. It is shown that ECD decreasing rates are significantly different than zero in all three periods.

By using two breakpoints, the magnitudes of the parameters are different than the FDA's results. The estimated ECD loss rate from three months to nine months is 17.63 per month, and the loss rate becomes 5.76 per month after nine months.

In the sponsor's model, ECD is also a significant factor. The sponsor also provided the predicted probability of ECD less than 1,000 at year four. For example, if a subject has baseline ECD equal to 2,500 and ACD equal to 2.5, the probability that the ECD would be lower than 1,000 is .149, and if

an eye has a baseline ECD equal to 1,600 and ACD equal to 2.5, this probability will increase to .644.

And our conclusions are, for the group IMT implanted eyes, ECD decreases throughout the study, slopes or rates of ECD loss of acute and chronic periods are both significantly different from zero.

At both acute and chronic periods the slopes are significantly different between the IMT eyes and fellow eyes, which suggests that there is a significant treatment effect in ECD change.

Thank you.

DR. CALOGERO: That concludes the FDA's presentation for this morning.

PANEL QUESTIONS FOR FDA

DR. MATHERS: Thank you.

Now we have a 15-minute opportunity for the panel to ask the FDA clarification, information, questions.

Dr. Weiss.

DR. WEISS: The loss of endothelial cell data is very compelling, as were the testimonies of those satisfied patients and the fact that there is not anything on the market to offer patients with this visual loss.

So the one slide that I would appreciate

more information about, and I found particularly disturbing was the slide from your presentation, Dr. Lepri, on adjusted versus actual acuities, because we're all being encouraged by the fact that many of these patients can see two lines or better. Your slide on page 11 of our handout which showed that an improvement of less than 1.4 or 2.3, because of the magnification, would really equal a loss of greater than two lines. This makes me wonder what we are talking about.

So did you have any estimates, using that, of what percentage of patients who we were - who looked like they were improving were actually getting worse, or the line that you indicate of the improvement of less than 1.4 or 2.3, how many patients or what percent of patients was that really entailing that might look like they were getting better but were not actually?

DR. LEPRI: This is Dr. Lepri. Dr. Drum will be addressing the response. That slide was prepared by him.

DR. WEISS: Okay, thank you.

DR. DRUM: Well, the problem you're having is exactly the problem we were having because we didn't have that information.

And we wanted your input on how important that additional information would be.

That question is assuming that nothing else is wrong, that the implant has been properly positioned, and is functioning as it's supposed to, and the remaining possibilities for why you wouldn't achieve the expected optical magnification effect would be some retinal problem or some other ocular problem.

And that's - I mean there may be other causes also, but we just don't have the information.

That would be fairly easy for the sponsor to get those numbers that you were asking about.

DR. WEISS: Do you think that it could be a quality of vision issue, so it could be something that patients might perceive an improvement even though this can't be measured? Because it's such a critical factor. If this measurement is sort of the end-all, be-all, and it's not sufficient, then that would mean that this wasn't efficacious.

DR. DRUM: The way I look at the issue is that using the preoperative acuity as a baseline gives you sort of a clinical efficacy measure; looking at the adjusted acuity gives you more of an indication of the effectiveness of the device.

I mean it's more of a - the patient is more interested in the former; FDA is more interested in the latter.

DR. WEISS: Thank you.

DR. MATHERS: Dr. Palta.

DR. PALTA: Yes, I would just like to get a little bit more detail on the statistics in more depth.

First of all you never tried the exponential model? Or was this based on a log scale, or was it on the original scale?

DR. YAO: It's actual ECD count. It's not - we didn't take the log scale.

DR. PALTA: But it seems like some of the literature fits either the exponential or the double exponential, and it seems that maybe that would lead to slightly lower percentages of ECD loss?

DR. YAO: You mean the bioexponential model?

DR. PALTA: Yes.

DR. YAO: We have checked the literature, and we compared our results with their results. Actually even though in the literature we saw exponential model was used, in ours, the parameter estimates was close to their estimates.

DR. PALTA: Even the extrapolation?

DR. YAO: Yes.

DR. PALTA: It didn't affect that very much?

DR. YAO: No.

DR. PALTA: And then when you said random effects, did you - what random effects were there? Like the intercept or the slope?

DR. YAO: Yes. The intercept - I put random effects on the intercept. Also the slopes.

DR. PALTA: Okay. And the percentages you showed, were those from the same model, or were those from a different model?

DR. YAO: From the same model.

DR. PALTA: So you modeled the variants at each time point from the random effects?

DR. YAO: Could you say it again? Sorry.

DR. PALTA: Okay, I was just wondering how you did that basically. You assumed a normal distribution?

DR. YAO: Yes.

DR. PALTA: And you had the random effects?

DR. YAO: Right, I had random effects on the intercept; also random effects on the slope, on the piecewise slopes. Then I used, based on my model,

the estimates of variances, I predict the ECD count for each patient; then at each time point of interest I counted the percentage of the eyes -

DR. PALTA: Oh you do it for each patient?

DR. YAO: Yes.

DR. PALTA: Based on some empirical base estimate then? Or just based on a line? Or how would that be?

DR. YAO: That's based on the individual -

DR. PALTA: You fit it to each person individually?

DR. YAO: Yes.

DR. PALTA: Okay, and then my final question was just, so that, did you have any idea of the confidence interval on some of those predictions?

DR. YAO: You mean the confidence interval for the mean ECD or confidence interval for the -

DR. PALTA: No, just it seems that the percentages that they're looking at are pretty close to the risk-benefit analysis. So was just would like to know how thorough those estimates are. I mean I know the extrapolation issue, but then in addition there is a random error issue, and I was wondering if you had any feel for the precision.

DR. YAO: The precision of the estimate, as

the parameters are pretty high precision. But if you wanted to look at the distribution of the ECD count instead of the population mean, it's kind of wide.

So you don't have to go beyond the two years. You will see a high proportion of eyes which would be 1,000 or lower.

DR. PALTA: Okay, thanks.

DR. MATHERS: Dr. Ferris.

DR. FERRIS: I just would like to focus back on this question of the expected improvement, and it seems to me that that's a theoretically expected improvement, all other things being equal, except these retinas are not equal, and they've got big holes in the middle of them in a sense.

So I would have been surprised if they could have all gotten the theoretical improvement, and maybe I'd just like to hear if that is what you are saying, or you were saying something different.

MS. THORNTON: Dr. Drum.

DR. DRUM: The other factor which the statisticians were just discussing is the possibility of measurement error which can be large in AMD patients. So if they happen to get a good acuity preop, on a good day, better than their average acuity, if they had taken a number of different

measurements, then they would have gotten less improvement from the magnification than you would expect, based on your measurements.

And conversely, some of the patients got a measurement - measured improvement of more than four or five lines, a few had six lines, and that could be measurement error, or it could be other change in fixation, locus, and stuff like that.

DR. MATHERS: Yes.

DR. FERRIS: So just to follow up on that, it seems to me I've been told by my low vision experts that multiple training sessions might improve your ability to function on some of these tests, and I wondered what you thought about that.

DR. DRUM: We agree.

DR. FERRIS: There are plenty of sources of error here.

DR. DRUM: We do insist that the training program is essential, and the better you validate it, then the more comfortable you are with knowing how effective it was.

MS. THORNTON: This is a period of clarification of what we have presented. So Dr. Lepri.

DR. LEPRI: I would like to address the

panel with respect to Dr. Ferris' questions here.

One thing to take into consideration in these low vision patients is that the majority of them are cataractous preoperatively and the refractions may not have been that accurate then.

However, when we remove the cataract we apply the telescope and then perform postoperative refractions, that the refractions improve, so that may account for a larger increase in the number of lines of improvement in acuity.

The information that I presented I presented to assist the panel to show them the literature relating to the fluctuation in visual acuity in this particular population. The proportion of individuals that achieve the mean visual acuity improvement so that that can be taken into consideration in defining the characteristics appropriate for a population indicated for this device.

Thank you.

DR. MATHERS: Any other questions from panel members?

DR. SZLYK: I was wondering if you had any data -

MS. THORNTON: Dr. Szlyk.

DR. MATHERS: Dr. Szlyk.

DR. SZLYK: Yes, similar to how you presented the data on page 10 of your - our handout for an analysis of functional improvement by visual acuity level? Given that there are so few individuals in the moderate impairment group, I'm just wondering.

DR. LEPRI: You say that's page 10 of your handout where you have six slides. If you had the slide number. We don't have that.

DR. SZLYK: Oh, I don't have a slide number. It's gain in visual acuity across visual impairment levels.

DR. LEPRI: You're referring to the data that was taken directly from the PMA.

DR. SZLYK: Right.

DR. LEPRI: And your question again, Dr. Szlyk?

DR. SZLYK: Relates to visual function, the NEI VFQ, if that were similarly divided by visual acuity level, impairment level.

DR. LEPRI: Well, what they showed on their VFQ results were that - and I think the industry here can correct me on this if I'm wrong - that they showed proportional improvement on the VFQ; that they had larger proportions, those with severe and profound.

Is that correct?

MS. THORNTON: We can deal with that later. This is FDA's turn.

DR. MATHERS: Right, let's go on.

Further questions from the panel? Dr. Weiss?

DR. WEISS: I would appreciate some clarification on the level of cataract, because I think that's really a confounding variable here, to determine how much is the cataract causing the visual improvement, and how much is not.

I know the question was asked of the sponsor, and as I recall, Dr. Bullimore said that cataract - you could not have a visually significant cataract.

As I'm looking through quickly and scanning the inclusion and exclusion criteria, I don't know if I'm not seeing that, or was that an exclusion criterion, a visually significant cataract?

DR. MATHERS: Dr. Lepri.

DR. LEPRI: Cataract is part of the indication. You had to have a cataract in order to have the IMT implanted.

DR. WEISS: Dr. Bullimore is sort of mouthing that he misspoke. So you could have - so

we'll take that out of the equation, the prior misstatement that you couldn't have a visually significant cataract.

So you did have a cataract. So how do we determine, is there any data here what the level of cataract in an individual patient was, whether it was 4+ nuclear sclerotic, half nuclear sclerotic, because certainly that would impact on the individual patient as far as their improvement.

DR. LEPRI: This is Dr. Lepri again. The majority of the patients, I believe it was over 90 percent, had nuclear cataracts, and then there were other combinations, combination of nuclear and cortical, and cortical.

DR. WEISS: Was the degree specified? Because a 34-year-old might have a 1+ but an 80-year-old might have a 4+ and they have different implications.

DR. LEPRI: I do not recall that any data was presented showing the stratifications of the degrees of nuclear or cortical pacification.

DR. WEISS: So that may be why it's impossible for us to decide how much is the cataract versus how much is the device?

DR. LEPRI: That's correct.

DR. WEISS: And it will remain impossible unless we had that information?

DR. LEPRI: Yes.

DR. WEISS: Okay, thank you.

DR. MATHERS: Yes, Mr. Bunner.

MR. BUNNER: Just thinking about from the patient's perspective, I know on the very last slide of Dr. Lepri's presentation, I know it's unknown, you have unknown problems with examination and treatment of an IMT implanted eye.

Was there anything during the study, and perhaps I missed that, of complications for the patient in the implanted eye? What might a patient expect on examination and treatment after the IMT?

DR. MATHERS: Dr. Lepri.

DR. LEPRI: The FDA's concerns with examinations postoperatively are the use of the typical devices used to examine the retina: binocular indirect ophthalmoscope; the direct ophthalmoscope. The sponsor did address some of that in their presentation by stating that they would dilate the pupil and they would also - and Dr. Lane mentioned about using a 90 diopter Volk lens at the slit lamp to observe the posterior pole of the eye, of the retina.

We had our concerns about other methods of

examining the retina, such as binocular indirect, which involve tilting the lens and the doctor tilting his head to observe the ora serrata and other more peripheral structures in the retina.

Those were not addressed about those examination techniques and should be something for the panel to consider perhaps in labeling or recommendations for physician instructions if they have more information.

DR. MATHERS: Is it the FDA's understanding that laser treatment of the retina after implantation would be precluded?

DR. LEPRI: Well, we don't have any -

DR. MATHERS: You don't have any data on that.

DR. LEPRI: I'm not presupposing anything. It's unknown, and that's why we say, these are some of the areas that were not addressed by how these things would be managed afterwards should they develop.

DR. MATHERS: Okay, let's adjourn this meeting now for lunch. We'll take a one-hour break, and begin again at 2:00 o'clock sharp.

Thank you.

(Whereupon at 1:04 p.m. the proceeded in

the above-entitled matter went off the record to return on the record at 2:06 p.m.)

DR. MATHERS: And I would like to reconvene our meeting.

This will be the panel discussion period. And we have three presenters.

The first presenter, or the first primary reviewer, will be Dr. Michael Grimmett. And then the - okay, we'll go through all three at one time.

Okay, Dr. Grimmett.

PANEL, PRIMARY REVIEWS

DR. GRIMMETT: Okay, thank you, Dr. Mathers.

They're hunting me down a laser pointer here, but nonetheless, we can start.

I just want to thank everyone for the opportunity to speak and present my comments on the implantable miniature telescope.

My comprehensive comments can be found in my written review dated July 6th. I'll try to highlight some of the issues in what follows.

I simply wish to point out here that - okay - nice, thank you. I simply wish to point out that other studies that track corneal endothelial health have 500 or more eyes in past applications.

This study has 206 at the outset with some loss over time with month 24 showing up at about 150.

Let's talk for a moment about posterior capsular opacification. Eight eyes in this study had PCO, two graded as moderate, and six graded as minimal. Two eyes required a needling procedure for the capsulotomy.

I just wish to point out that the coherent YAG was approved in 1984. Most ophthalmologists currently in practice will have no idea how to do a needling procedure. I've never seen one; I've never done one.

We're told that we can't YAG through the optic of an IMT. A circular YAG is suggested around the telescope optic. In rabbits it took 100 to 138 bursts to complete the capsulotomy. That's quite a bit more shots that a standard diamond shaped capsulotomy in my hands perhaps 25 bursts.

We know that the risk of retinal detachment in a YAG die is fourfold higher than a non-YAG die. The question remains, do the high number of bursts for this procedure increase the retinal detachment risk?

Also, a circular capsulotomy may cause a very large vitreous floater.

Had a slide in here on glaucoma to keep Dr. Heuer in the game here.

There were transient IOP elevations in day one in about a quarter of patients likely related to viscoelastic. Published literature shows that sulcus placed IMT haptics can narrow or close the angle.

Despite this fact I couldn't find gonioscopy data in this PMA, and we learned that perhaps four percent or so of haptics were sulcus placed.

Also, I wonder if the pigment deposits on the IMT in 7 percent translates to chronic iris chafing with possible pigment dispersion syndrome.

Several routine eye care issues are affected by the IMT. Angiograms are reportedly burdensome due to glare and a small image size.

Additionally both peripheral retinal examination and peripheral retinal laser can be limited, especially in patients with iris optic adhesions.

There was one reported case of argon laser to the macular through an IMT, I believe it's by Garfinkel. It was challenging due to the small image size. In the rabbit study argon laser was not possible.

Is a retinoscopy possible in an IMT eye? I don't know. Can you do an OCT for macular disease in an IMT eye? I don't know.

All of these issues will affect routine eye care in an IMT eye.

We've already heard about effectiveness data both from sponsor and from FDA. Therefore, I'll limit my comments to one particular issue.

In the IMT trial, according to FDA presentation, the patient was largely responsible for implementing a rehab program with family assistance.

In draft questions FDA was going to ask this panel if a vision training program should be a requirement, or simply a recommendation.

Dr. Lane, the medical monitor fo this study, wrote that a visual rehabilitation program led by a vision rehab specialist is a key factor to a successful outcome with the IMT device.

Other investigators have other similar published comments including the word, mandatory. I agree. The labeling should be a requirement.

On to the corneal endothelium. For a consistent cohort of 130 eyes there was a 20 percent decline in endothelial cells by month three; acute surgical trauma that increased to about 28 percent at

the two year point.

First, how close is this device to the cornea? From a cornea proximity standpoint the IMT is analogous to an angle supported phakic IOL. Some background first.

The corneal endothelium seems to tolerate a fourth-generation angle-supported IOL; this is ESAL-4, with a 2.4 millimeter central distance, and a 1.6 millimeter peripheral distance.

Those might be okay. The corneal endothelium, on the other hand, does not tolerate a peripheral optic endothelial distance of 1.2 millimeters; that is, the first generation Baikoff ZB lens.

In general the closer an optic is to the corneal endothelium, the more risk it presents for chronic trauma.

In the PMA presented to the FDA and us, there is no data about optic endothelial distances, particularly in eyes with narrow anterior chambers: no ultrasound measurements, no slit-lamp measurements.

It's important to recognize that the ultrasound data shown today in one slide in sponsor's presentation is not been previously submitted for independent review by this panel.

They showed a central distance of 2.54, and a peripheral distance of 2.18. The range of anterior chamber depths was not known; that is, how narrow did they go.

With all due respect to sponsor, their slide of ultrasound images in seven eyes at one center is not likely representative of the entire cohort. Their slide merely shows that it's not at an unsafe distance in some eyes. But it does not show that it's a safe distance in all eyes; an important distinction.

Where does the IMT sit in eyes with the narrowest anterior chambers? That's the relevant question.

Let's look to the published literature. Two cases in the published literature had one haptic in the sulcus and one in the bag. In case one, shown here, the peripheral optic endothelial distance range from 1.2 to 1.4. The sulcus haptic was 1.2 over here - here's a sulcus haptic right there - and the bag placed haptic had a peripheral optic distance of 1.4. The central was 1.5. The preoperative anterior chamber depth was 3.22.

These close distances mimic the first generation angle supported phakic IOLs, lenses that were unsafe and led to marked endothelial cell loss.

Case two had a peripheral optic endothelial distance as close as .967 in the area of a sulcus placed haptic with an IMT tilt.

And there was also partial angle closure near the sulcus-placed haptic. This eye can be expected to have chronic cell loss from ongoing endothelial trauma.

In the IMT study we know that two corneal transplants were performed. Both eyes had anterior chamber depths less than three millimeters, and sulcus IMTs in both.

The IMT optic was likely too close to the endothelium in these cases, based off the published data we just saw.

Another study measured the IMT distance using a slit lamp and 40 eyes. The mean was 1.71, plus or minus .2, with a minimum of 1.

It didn't specify central or peripheral distances; was not stratified by the anterior chamber depth; three of them were not in the capsular bag.

Based on these data the IMT endothelial distance is barely sufficient. Some eyes probably have dangerous proximity of the optic to the endothelium.

To assure long-term safety of this device

I'd recommend that the sponsor should supply ultrasound measurements to the FDA, central and peripheral, in a representative number of eyes stratified across anterior chamber depths, particularly narrow ones.

Two models for endothelial cell loss have been proffered one by the FDA, and one by the sponsor. Let's look at each.

The FDA model is a two-slope linear model. There's about a 21 percent loss by month three, and a six month loss thereafter.

The three month breakpoint is supported by published studies of large incision cataract surgery. The coefficient of variation in percent hexagonality generally returned to baseline levels by month three.

The sponsor's model for endothelial cell loss, on the other hand, is a three slope model, baseline to three months, three to nine months, and nine to 24 months.

I was unable to find published literature that analyzes endothelial cell loss for the three slope model.

I was also unable to find morphometric data in the PMA to justify the sponsor's choice of breakpoints.

Moreover, the FDA did not unresolved problems with this model, for example using the nominal visit time instead of the actual visit time, among others.

In short, sponsor's model predicts a lower rate of chronic endothelial cell loss after month nine, a 39 percent decreased rate compared to FDA's model. It's presenting the data in its best light.

We need to know whether the endothelial loss is due to remodeling or whether the endothelial loss is due to a chronically stressed endothelium due to the IMT device.

Endothelial cell migration that is remodeling occurs after surgical trauma to the eye. It can occur for prolonged periods.

With remodeling, the coefficient of variation and percent hexagonality return to baseline levels and do not show progressive deterioration.

On the other hand an unstable or chronically stressed endothelium will have abnormal morphometric values that do not return to baseline.

Morphometric data are a more sensitive indicator of endothelial health than central endothelial cell density measurements alone. This has been known for more than 20 years.

Surprisingly, the sponsor's PMA does not include any morphometric endothelial data, a critical deficiency in my mind.

In short, IMT's have cell loss 2-1/2 times higher than the pseudophakic eyes. We need to know whether the endothelial loss represents remodeling or a chronically stressed endothelium.

Published optic endothelial distances make it conceivable that the IMT device causes an unstable endothelium, at least in some eyes. For this device it's mandatory to obtain morphometric data to ensure that the coefficient of variation and percent hexagonals return to baseline levels within a reasonable period of time. We have none.

I am surprised that the IMT study was designed with only central endothelial measurements. Since the mid-1980s peripheral measurements were known to be valuable when analyzing endothelial remodeling after large incision cataract surgery.

The superior cornea particularly may act as a reserve for remodeling. It has a 16 percent or so increase cell density versus the central cornea.

The IMT procedure, we learn, uses a large superior incision, 12 millimeters or so, and implants a bulky device from a superior approach.

These factors will probably harm the superior cornea, the largest reserve for remodeling.

I'll bet that peripheral endothelial measurements would help us analyze the safety of this device. Regrettably, none were obtained.

A quick word on pachymetry. Pachymetry reflects endothelial cell function by measuring corneal stromal hydration. Regrettably, pachymetry was not routinely measured at the postop examination intervals, nor was it reported in the PMA materials, despite its relevance to corneal endothelial function.

Let's look at preop exclusion criteria as they apply to following corneal endothelial health in a study of this kind.

Several things can affect cell density in endothelial morphometric data. For example, diabetes, glaucoma, contact lens wear. Without going into the specifics, for this study diabetes was not a listed exclusion criteria, and neither was contact lens wear.

Controlled glaucoma patients could be enrolled. Granted, 75-year-old macular degeneration patients with cataracts are not likely going to be wearing contact lenses. However, I'm simply surprised that relevant confounding factors for endothelial compromise were not specifically excluded at the

outset.

A word on chronic inflammation in endothelial cell loss. Chronic inflammation is a known factor in ongoing endothelial damage. The IMT device causes a significant amount of inflammation.

Number one; the device requires very high dose topical steroids, a subconjunctival injection of steroids, cycloplegia, which is continued over three months. That's much more than standard cataract surgery.

Number two; In the phase one trial Lane noted that the most notable complication was late intraocular inflammation.

Number three; the IMT study reported inflammatory deposits on the IMT in 13 percent of eyes at 18 months.

Number four; there were pigment deposits on the IMT in seven percent which may be a sign of chronic iris chafing, with subsequent breakdown of the blood-aqueous barrier.

Based on these factors I'm unable to rule out chronic inflammation as a cause of ongoing endothelial damage in at least some of these IMT implanted eyes.

A few comments about anterior chamber

depth and endothelial loss.

The main anterior chamber depth was 3.15, plus or minus .37, with a range of 248 to 474.

We know that shallower chambers adversely affect the endothelium through two mechanisms. One, increased endothelial trauma during IMT insertion; and two, the optic is closer to the endothelium, possibly causing trauma.

There was a trend for higher cell loss for shallower chambers. This is a similar table to what Dr. Lepri showed earlier in FDA presentation, taken from Vision Care Table A-29(b).

Given the two mechanisms for trauma just mentioned, it's probably prudent to exclude narrow anterior chamber depths to protect the corneal endothelium.

Sponsor's table A-29(b) I want to point out says that these are not statistically different. They ran a nonparametric statistical test. But I want to point out that the group sizes are not large. At the 24 month interval here there were probably only 23, 25 eyes. The group size, if it were larger, would increase the statistical power.

Additionally we know that anterior chamber depth is a continuous variable. Grouping them into

these fashions may not properly describe the statistical test they were trying to do.

Mean central endothelial cell density loss, let's take a closer look. I did find it reassuring that the study closely matched known loss rates for both pseudophakic and unoperated eyes.

For pseudophakic eyes in the IMT study they found a rate of 2.44. The known rate is 2.5.

For fellow phakic eyes they found about a 1.06 percent annual loss rate; known rate is .6 to 1.

Given these findings I have no reason to doubt the IMT endothelial loss rates reported in the study since the methodology for endothelial cell analysis, whatever it was, must have been identical across all eyes - phakic, pseudophakic, or IMT implanted.

The most notable feature of the IMT PMA is the large endothelial losses over time. They are substantially more than standard large incision cataract surgery.

The IMT study had a 21 percent acute loss versus an approximately 12 percent acute loss following large incision cataract surgery.

As previously shown this particular figure can vary depending on what study you look at. A

recent study by Bourne of 250 eyes showed a figure of about 10 percent for extra caps.

The IMT study also had a six percent chronic annual loss rate versus a 2-1/2 percent yearly loss rate following large incision cataract surgery. That is, a 2-1/2 fold increase rate. Incidentally, the IMT chronic loss rate is 10 times higher than unoperated eyes.

What are the minimum cell density values for corneal clarity? In August 2002 Dr. McCarey identified a cell density of 1,500 as the quote unquote minimally acceptable level if an eye is to undergo a future operation; and also stated that a cell density of 800 is the threshold for potential corneal edema.

In the 2005 Procter Lecture, Dr. Edelhauser (phonetic) reported possible endothelial decompensation with cell densities less than 700.

Using cell loss rates from the FDA model I calculated required entry cell counts to live the average projected lifespan with an 800 cell count at the time of death. I used instantaneous annual exponential losses, and rounded down fractions since partial cells are not viable.

The table shows that a 60-year-old, for

example, up here, must have a cell count of 3984 in order to die with a cell count of 800 22 years later.

Well, that's not possible. The average 60-year-old will have about 2,700 cells. It's also unlikely that we're going to find a 65-year-old having 3,106. However, after age 70 we might find patients with these entry cell counts. But please recognize, purely looking at it from the mean does not describe all outcomes.

After IMT implantation the standard deviation of the mean endothelial cell density increase by about 70 percent. Let's take a look.

This is a plot of cell densities with time that we've seen before. Many eyes are pushed below 1,000 as a consequence of an increased spread of the data, tighter baseline spread here, increased spread here postop.

Hence, simply following the mean cell density does not adequately describe many adverse corneal outcomes that impact a significant number of eyes.

Using the FDA model for cell loss, if the baseline cell count was in the lowest quartile a whopping 39 percent, end up with a cell count less than 1,000 in only four short years.

Additionally almost a quarter of all comers will end up with cell counts less than 1,000. That's corneal edema territory, or on the way.

Recognize that a 75-year-old has a projected lifespan of 12 future years. If the rate of chronic cell loss does not slow down, we could be seeing a epidemic of corneal edema not long after implantation of this device.

Sponsor's model, the model that casts the best light on the chronic cell loss, also predicts worrisome figures for cell counts less than 1,000 in four years. Shallow anterior chambers fared worse across all categories.

Number two, entry cell counts of 1,600 have an unreasonably high risk of entering corneal edema territory at year four, a risk that increases with time.

About a third of eyes, range 24 to 40 percent, with entry cell counts of 2,000, cross over into corneal edema territory at year four. And the best circumstance of an entry cell count of 2,500 still causes seven to 15 percent of eyes, about one in 10, entering corneal edema territory by year four.

Based upon these data I'm very concerned about the safety of this device from a corneal

endothelial standpoint. A significant proportion of eyes can be expected to develop corneal stromal edema during their lifetimes, unless the entry cell criteria are limited, or unless the chronic endothelial cell loss decreases with time.

As far as approval is concerned, the sponsors left me guessing due to missing information. I simply don't have the necessary data to make the call.

Morphometric endothelial data are needed to diagnose a chronically stressed endothelium versus prolonged remodeling. The morphometric data need to be stratified by anterior chamber depth, with particular emphasis on narrow anterior chambers.

If the morphometric data are consistent with an unstable endothelium the device is unsafe; and therefore, not approvable.

If however the morphometric data are consistent with ongoing remodeling, it is conceivable that the cell loss rate may also slow down to approach pseudophakic rates, and for that circumstance the entry criteria must be limited to reduce future risk of corneal edema; that is, restrict shallow anterior chambers, perhaps three millimeters, although the data grouped in those fashions are fairly arbitrary.

Number two, set a minimum entry cell count: 2,500.

Set a minimum entry age: 75 years old.

Or perhaps create a sliding scale of baseline cell counts for given ages consistent with life expectancy tables. That has prior precedent with other PMAs.

Also, as previously mentioned, the sponsor should additionally submit sufficient ultrasound data stratified by anterior chamber depths.

Both central and peripheral distances are necessary. Eyes with narrow chambers are of particular interest. Based upon angle supported phakic eye wall studies, if the peripheral optic endothelial distance approaches 1-1/2 millimeters we should limit the entry anterior chamber depth accordingly.

Additionally if the device is ultimately approved with conditions in the future, new surgeons should start with deep anterior chambers. Labeling should strongly state the device is unsafe when placed in the sulcus, since it's dangerously close to the corneal endothelium.

If known at the time of surgery, the device should either be repositioned within the

capsular bag or explanted.

And number three, future specular photographs if any should include a peripheral measurement, particularly from the superior cornea.

That concludes my introductory comments. Thank you so much for your attention.

DR. MATHERS: Thank you, Dr. Grimmett.

Now our next presentation will be from Dr. Neil Bressler.

DR. BRESSLER: Thank you, Dr. Mathers.

I want to thank the FDA's staff for providing all the information to help us do this review. I want to thank the sponsors, because I believe they have taken on an attempt at a major public health problem. We certainly would like to rehabilitate people who have lost this vision.

The review that I did that's summarized in your book there identifies several methodological concerns, and these concerns led me to question the validity of the results, and maybe some of them can be addressed when we discuss it. And I think it's important to resolve these in order to be able to understand if it's effective or safe.

So what are some of the study design limitations?

Number one, there are no controls. You don't have to have controls with every study you do to determine if something is safe and efficacious, but in this condition I think we do.

Without the controls it's impossible to determine if the visual acuity outcomes that we see are actually worse than might occur if you didn't have the implant placed in.

You might say, how could that be? Well, because these people also underwent cataract surgery, and maybe they would have improved at that point.

These people also underwent rehabilitation. So if they had been randomly assigned to getting their cataract surgery and rehabilitation only compared with getting their cataract surgery, rehabilitation and the IMT, we might know what is actually due to the IMT itself.

For example, I mentioned that the visual acuity improvements were noted in about 73 percent of cases improving two or more lines. All of these underwent cataract surgery. All of them underwent rehabilitation.

It's possible that maybe 95 percent would have improved by two or more lines from baseline at 12 months just from the cataract surgery, a standard IOL,

and rehabilitation about how to use their vision peripherally, or as they get used to using their vision peripherally from their scarring.

So maybe that would be 22 percent were harmed, just as an example.

A similar limitation exists with respect to interpreting the NEI-VFQ requests. We know that even with no treatment NEI-VFQ can improve over time, because people adjust to the problems that they have with these stable discoform scars. But the improvement again could be due to the cataract surgery or the rehabilitation or both.

So I think the results are not overwhelming enough to be able to allow us to conclude anything about the effectiveness in the absence of controls. If everyone had improved to 20/20 and was walking around with no problem then that would be a different story.

But at the level of vision we saw, in terms of 73 percent improving two or more lines, that's not enough to know if that's just the cataract surgery, the rehabilitation and the time over one year, without controls.

The second item is easier to address, and that is that the analysis admits the outcome of the 11

eyes that did not have a successful implant placed. And although this is only 11 eyes, it's 11 important eyes, because we need to know what happened to their vision when this occurred

You count discount that, I believe, when you're looking at the effectiveness. This would be like taking any sort of device, and let's say 90 percent of the people undergoing some surgery had a bad out outcome, and you eliminate those and you only pay attention to the 10 percent that had the successful outcome at the end of surgery, you wouldn't necessarily recommend that device, because you'd still have to deal with the 90 percent that you didn't know were going to have the problem.

Well, it's not that extreme here. It's only 11 of the 217 eyes. But nevertheless, I think we need to know and include that in the safety, before you bring them to the operating to have that implant, they're included in there.

The sponsor indicated that they were giving the results of these successfully implanted IMTs. When I went back to look at the protocol, the protocol said that they were going to look at the results of people undergoing implantation. It didn't mention the adverb, successfully implanted. I only

saw that after the results. So I'm not sure that that was the intention of somebody reviewing it at the onset, but certainly that was the intention of describing it later on.

So I think we need the information, as much information as possible on those 11 eyes.

In addition the third limitation is that there were several eyes, eight of them, that had the implant removed over time. And we don't necessarily have their information all the way out to 12 months.

But those people might be cases that didn't do very well. They may have had corneal edema. They may have been the ones that needed a transplant afterwards, because of endothelial decompensation, or other reasons that the implant had to be removed.

And if we don't have that information, that could easily increase the - what was 5 percent in terms of their primary outcome for visual acuity with the 11 cases that did not complete the implantation, with these eight cases that did not - that had the implant removed over time, that could easily bring you over the 10 percent that they chose a priori that they had to meet in terms of avoiding two or more lines of loss with distance and near.

It's also unclear as we mentioned during

some of the questions what was done with the missing data so far. And missing data is difficult. And fortunately the sponsors didn't have many people lost to follow up. But when we're dealing with just 10 eyes or 13 eyes that are lost to follow up by the one year, in a disease that potentially is progressive. It may be that the endothelial cell loss was greater in the people that were not still coming back. They may have had some interference with their vision later on, and may have lost some vision later on.

So I do think that we have to look at the missing data and take that into consideration, and impute it in several ways. Look at the observed data that's available. Look at what it would be if last observation was carried forward. Look at what it would be if those cases had failed, if they had lost two or more lines for example.

I thought the NEI-VFQ information was important. We didn't have controls as I mentioned.

I didn't know what to do about the activities of daily living. It said that this questionnaire was modified from the activities of daily vision scale. So I didn't see any references to explain what this modification was, and if this modification had been validated. So perhaps we have

some experts, or people know if this modification from the daily vision scale to what they used, which was the activities of daily living, is indeed validated, and what would be considered an important change for that.

The incidence of posterior capsular opacification was a little confusing to me. It was confusing because when I looked at the case report forms and again, I might be missing something here so I'm bringing it to the panel so we can discuss it, I didn't see a specific checkoff at the follow up to indicate if there was posterior capsular opacification or not, so I didn't know if that had to always get checked off under other.

If it had to get checked off under other, then I always worry that maybe somebody wasn't purposely looking for that. We do have these eight eyes that were reported. In the slide that was reported today, it said operative and perioperative complications. But I don't know if that includes the follow up. So that needs clarification, but I couldn't find that, so I'm worried that maybe we are underestimating the posterior capsular opacification that was reported if it was not systematically asked for.

When the sponsors responded to deficiency 15(c) that was in the December 8th, 2005 letter - this is the one that dealt with, is the sponsor aware of the nystagmus disorientation or other vestibular problems that might occur? And the sponsor was asked to clarify whether this was questioned. And it was not questioned.

The sponsor indicated that, well, although it was not questioned, this was not a complaint to any of the eyes that were explanted. But again, if we don't ask the information, we may not know if it's there.

We heard from the public statement that Doyle said from Emery that the low vision person indeed saw some cases of difficulty improving from three months onward. And I don't know if this information was collected where it was a problem at three months and then went away. But since we didn't have any information about it, even the information that was in that public letter that was reported to us makes me question that we may not have gotten all that information.

And finally I didn't have a good feel from the information that was presented - it's either in there and I couldn't pick it out, or we just haven't

gotten it yet - as to what the total of additional procedures that were done from the data provided.

I couldn't get a good summary of how many corneal transplantations, retinal tears, retinal detachment, cryopexy, anything else, I couldn't find a good summary of all the procedures that had to have been done in this group, so that we could at least compare to historical controls as to how many procedures get done after cataract surgery.

So I have difficult, in summary, evaluating the effectiveness because of those limitations.

In terms of the safety, specifically, I'm out of my area of expertise. I learned more about corneal endothelial cell loss by doing this than I'd ever known before, so all I'll say is that a 17 percent cell loss density was chosen a priori at the start of the trial. I don't know if that's the right amount, or not the right amount, but that was not met.

So when people got together, experts I presume, said, we don't want it to be greater than this, because we're concerned; it was greater than that. So if they were concerned, I'm concerned.

I don't think there is sufficient power right now to be able to divide this out into the

anterior chamber depth. There just isn't enough cases so far to do that; that I know, to do that.

I thought there was insufficient information as Michael already mentioned about the YAG capsulotomy, and I think this is important, but again, I'm concerned that we don't know how many posterior capsular opacifications had occurred, and many of these could still occur between years one and years two that we don't have yet.

The potential problem with MRI was interesting, because, of course I hadn't thought about that until I read about it in the materials that ere given to us.

I understand that there is another model being considered that would avoid the materials that are in there that cause an MRI problem. But I would be very concerned if there's a theoretic risk of MRIs spinning something around inside somebody's eye before we know about it. And maybe you do have to wait for the other model to be available. You cannot predict in a 75-year-old who's going to need an emergency MRI for a variety of medical problems, stroke especially. So I thought this was a problem.

I only had some minor other comments at the end of your discussion. At some point I think we

want to clarify how people got in with only druzen (phonetic). There were three cases. But I think this indicates that there could be significant cataract, because if somebody didn't have choroidal neovascularization, if they didn't have geographic atrophy, they shouldn't have significant vision loss from macular degeneration. There were only three eyes in that, but there were three eyes.

The materials state that a five point change is clinically relevant on the NEI-VFQ. This might be a little low. In the age related eye disease study, report #22, they indicated that a 15-letter loss, or the development of neovascularization, is probably associated with somewhere between seven, eight or nine point change on the NEI-VFQ, so five might be a little low for doing that.

The sponsor recommends that no treatment for AMD should be needed over the past six months. This will be a problem in the future, because we now have much better treatments for choroidal neovascularization than we had at the start when this trial was done. And it's very possible that people with geographic atrophy who might get this telescope could develop choroidal neovascularization still, and they would certainly benefit by treatment. But we

have to be able to identify that it's there, and we don't have evidence yet that that can be identified pretty well, because we don't know what it's like to do fluorescein angiography through this and reliably interpret them to be able to identify those diseases.

Also we don't have documentation as to what was going on with the definition of macular degeneration. At the beginning of the protocol it said they could come in with a dystrophy, which would be Stargardt's dystrophy, and I don't know if the geographic atrophy that was enrolled was due to that, because then everything else we were told was age-related macular degeneration that might have been changed later on.

Finally, the near visual acuity I'm not sure how that's been calibrated, or how that's been validated in terms of measuring the near visual acuity, and it would be nice to have some information.

So just in conclusion, as I mentioned, the biggest limitation I had was in the study design, because it did not allow me to have enough information to evaluate the effectiveness because of the lack of controls and the information that was removed from the cases that were not successfully implanted, or that had the implant removed later on, and then the safety

issues I've already discussed. And I thought Michael summarized them very well, so we can discuss these later.

Thank you.

DR. MATHERS: Thank you, Dr. Bressler.

Our final reviewer will be Dr. Richard Brilliant.

DR. BRILLIANT: Thank you, Dr. Mathers.

We do know as the population gets older there is more potential for individuals with decreased vision.

We do know that ARMD is the leading cause of legal blindness for those individuals 65 years old or older. And we do know for age-related macular degeneration, atrophic type, dry type, that there is no known cure.

So in order to help these individuals for the most part to function a little bit better, we basically have to use low vision techniques, which comes down to magnification, and magnification does nothing more than enlarge the image on the retina, making it easier for patients to see things.

There are basically four different types or different approaches to magnification: relative size, projection, relative distance and annular.

Relative size is nothing more than making things larger, keeping it at the same distance. In other words going from a 20-inch TV to a 40-inch TV will provide two times magnification.

Projection magnification is nothing more than projecting small print for the most part onto a screen similar to what we're doing here with PowerPoint, and that's found with reading machines, closed circuit TVs that are used for low vision patients for reading.

Relative distance is nothing more than you're getting closer to the object concerned. So if we had a TV at 20 feet away, and we walk up to 10 feet to look at the picture, we're actually producing two times magnification there.

And angular magnification is basically looking through a magic black box in which the rays of light entering this magic black box leave with a greater angle, so therefore the ratio of the angle of incidence to the angle of emergence determines how much magnification this black box is producing.

And this black box is nothing more than a telescope.

A telescope is the most commonly prescribed device for distance activities. The

magnification is determined by the patient goals or visual concerns.

The goals actually drive the exam. So we have to determine on any patient what their goals are before we can determine how much magnification or what type of telescopic system to go to if we decide a telescope is to be used.

If the person has goals that are general goals, we generally determine that the target acuity is 20/40 to 20/50 acuity. With this acuity we feel that an individual could do most activities. They could drive a car. They could watch TV. They could read street signs for the most part at a reasonable distance.

So 20/40 or 20/50 has been pretty much established as the standard visual acuity for most low vision patients for the doctor to try to achieve that acuity for the patient through the use of a telescope.

There are a wide variety of refracting telescopes available at this point. I don't think there is any reason to go into all those at this point.

But when we prescribe a telescope, we want to measure the advantages and disadvantages, and make sure that we're prescribing a telescope that has more

advantages than disadvantages.

For the most part the implantable miniature telescope is nothing more than a Galilean refracting telescope. It's available in two magnifications, 2.2 and 2.7X. It's a binocular system, meaning you use one eye for the magnification, and one eye that's not magnified.

As far as I could determine from the literature, the advantage of the implantable miniature telescope over an external telescope is the fact that cosmetically perhaps it's more pleasing, because it is implanted inside the eye and therefore the person doesn't have to be holding a telescope with this magic black box. Or there are some individuals that wear a telescope mounted into a pair of glasses. And again cosmetically that sometimes is unpleasant.

Also weight becomes a factor with some telescopes. If a person is wearing a telescope for any length of time, weight does become a consideration. Some patients will complain about the fact that that weight on their nose becomes uncomfortable.

The implantable miniature telescope was tested over a two-year period of time, the literature says, and a majority of subjects achieved improvement

in best corrected distance acuity.

Sixty percent of those achieved improvements of at least three lines. And when you use a log mark chart, by improving in acuity three lines, you're doubling the acuity; you're doubling the vision of an individual.

So one of my concerns here is the fact that only 60 percent of those individuals are achieving at least a doubling of their acuity when looking through a 2.2 or 2.7X telescope.

Some of the concerns I have also are the fact that if a patient is implanted with the telescope, and his or her vision decreases to a point requiring more magnification, then that might cause additional surgery, and the cost and the risk of surgery is a factor.

Plus, more powerful systems are required, so therefore the individual would have to use an external type of telescope if they have to go to a more powerful system, because the implant only comes up to 2.7 times magnification.

As far as I'm concerned, everything I've read, it appears that the subject's specific visual concerns were never considered in determining if he or she was a good candidate.

I commend the research department in doing a quality of life and activities of daily living questionnaire, which was presented to each patient.

The results of the quality of life questionnaire showed general vision improvement to be the greatest response, followed by near vision activities, and distance vision activities.

The thing that concerns me here is the fact that general vision improvement was considered the number one thing. And I think that if you put any telescope, whether it be an external or an implanted telescope, in front of any patient, you're generally going to get visual acuity improvement. And most patients will say yes, their general vision has been improved.

The thing that I find most noticeable is the fact that the distance vision activities is dead last out of these three things. And the telescope is basically meant for improving distance vision activities; so that's a concern.

Since visual concerns did not appear to be utilized in determining the need for specific telescopes, my question is, how was it determined which patient got a 2.2X telescope or a 2.7X telescope?

And also it never says or states in any of the information that any of these individuals were shown external telescopes prior to have this implant other than having that 2.2X hand-held placed in front of them.

But they were never shown a large array of different telescopes that might provide them with better acuity and better function.

With the available magnifications of only 2.2 and 2.7 there appears to be a limited number of patients who may truly benefit from such a system. Suggested patients for this study with moderate to profound loss for those individuals with 20/80 to 20/800 visual acuity.

In reality only those individuals with 20/80 to 20/140 may truly benefit from this telescope.

It's a little difficult to see, but I did do a table here that predicted the distance visual acuity through a 2.2X and a 2.7X telescope, and when using a 2.2X telescope we could see that if the person's visual concerns are to be addressed - and again we state that 20/40 to 20/50 visual acuities are the acuities to concentrate on - we see that individuals up to about 20/110 or here 20/120 will produce significant visual improvement so that the

person can function to do certain tasks.

With a 2.7X up to about 20/140 with the use of a 2.7X will produce 20/51 acuity.

The remainder of those acuities for the most part the telescope will certain improve visual acuity, but are they really improving visual acuity in allowing the person to function with certain tasks?

Therefore visual function is more complex than just the ability to read letters or numbers on a chart. Reading isolated high contrast optotypes in a dimly lit room does not necessarily correlate well with the number of visual tasks that individuals have to perform on a daily basis.

And this is a little ironic, but a perfect example was on Wednesday I had seen a patient that had been brought in by her two daughters. And she had just read an article about a patient that had received a telescope from our clinic as a matter of fact who had listed in the newspaper 20/400 acuity, and this person in the newspaper was making these claims that this telescope allowed him to watch TV much more comfortably; to watch ballgames; to actually go to a ballgame and see some of the activities that were occurring on the field.

When we checked with this particular

patient who was coming in, we found that her vision was actually 20/320, and with this 2X telescope her vision did indeed improve to 20/160, and she was thrilled, and her two daughters who were sitting in the examining room where thrilled by this. And it was exactly as we had anticipated, a 2X improvement.

However, when we put her in front of the TV, her comments were that things looked larger; it was a little easier to see; but it still wasn't comfortable; and it still didn't allow her to see any of the detail on the TV.

We allowed her to sit even closer, focusing the telescope so that it will accommodate for that closer distance. It got to the point where we brought her so close that the field became a problem, where she wasn't able to take in the whole TV.

So in reality what happened here was, even though we were able to include the person's visual acuity, functionally the person wasn't able to accomplish the task that she wanted to accomplish.

Needless to say, she was a little upset about the whole thing, and so were her daughters, and we ended up having to go to a much higher magnification, 5.5, in order to solve the problem. So that wouldn't have been done by this implantable

telescope.

When we talk about near acuities, again, we're looking at the same thing. We think that most individuals would require anywhere from 20/40 to 20/50 visual acuity improvement to be able to read standard size print. The reason we say that is because if you actually measured the physical size of newspaper print, it's pretty much equivalent to the 20/50 letter. And therefore in most cases that ends up being our target acuity when individuals want to be able to read.

The difference is, there's a big difference between visual acuity and reading acuity. Visual acuity is basically evaluating individual optotypes, and therefore, easier to see than words, sentences and paragraphs. Spacing between letters, contour interaction, contrast of the letters in the background, and uniformity of the print size, makes it a little more difficult to read print than it does reading a visual acuity chart.

I also want to note that if we calculate out how many - the equivalent power of these system, the 2.2X focused at 16 inches, a 2.2X focused at eight inches, a 2.7X focused at 16 inches, and a 2.7X focused at eight inches, we come up with the

equivalent diopteric power of 5.5 diopters, 11 diopters, 6.75 diopters, and 13.5 diopters respectively.

Now what does that basically mean? What I'm saying is that with the use of this telemicroscope, and a telemicroscope is nothing more than a telescope with a reading lens, and you have to use a reading lens in combination with this implantable telescope to be able to obtain a focus at 16 inches or at eight inches.

So if we calculate out the equivalent power of this combination of telescope and reading lens, we find it's producing no more than 5.5 diopters, or 11 diopters or 6.75 diopters or 13.5 diopters.

That could easily be given in a pair of reading glasses and solve the problem a lot easier and probably the individual would probably adjust to a pair of reading glasses at lower power much easier perhaps than a telemicroscope which is more demanding as far as the depth of focus is concerned.

Also the field of view would be much larger in a reading lens than it would be in the equivalent power telemicroscope.

It was also reported in the FDA executive

summary that the sponsor argued that less than the theoretical improvement should be expected clinically because of the reduced central vision in the study subjects. And we discussed this earlier today.

Patients should theoretically, and they do clinically, respond pretty much as you would expect. If a person has a 2X telescope put in front of them, you'd expect that they'd get very close if not exactly two times improvement in visual acuity.

If they're not getting that improvement, then there are certain things that you should be looking for, perhaps eccentric viewing, the alignment of the telescope, contrast or illumination differences between the visual acuity charts in the exam room when you're taking an acuity one time or another; if the chart is on wheels, or you're able to bring it different distances, was the distance slightly different measuring it one day versus another day, or going from one exam room to another exam room; the test takers, very important, might have been using different test takers at different intervals when you were checking the visual acuity. Different test takers will push a patient differently.

The mood and willingness of the subject to respond. Some patients will feel that they have to

get every word, every letter or number on that chart perfectly right before they'll give you an answer. Others are willing to take a chance and read off whatever acuity they might think they see there.

The one thing I have found is that it's not uncommon for a low vision patient to read a whole line, read that accurately, and get to the next line and say they can't see it. That's pretty much impossible. If they've read that whole line accurately, they've got to be able to read some of the letters or some of the numbers on that next line.

So again the mood or the willingness of that subject to respond is an important factor.

Certainly an uncorrected refractive error might account for difference in acuity, and ocular complications of course have to be looked at.

It was recommended that if the best corrected vision was better than 20/200 in either eye, the eye with worse acuity would be chosen for the implantation.

Why wouldn't you want to put the telescope in the better seeing eye to achieve maximum benefit for that telescope? As long as that fellow eye had enough peripheral field for mobility purposes, I don't see any advantage of putting that telescope in the

worse seeing eye.

Why wasn't a team of professionals - low vision specialists, occupational therapists, occupational therapists used to help recommend what eye the telescope might be implanted in?

Prior to surgically implanting the telescope it does not appear that a thorough binocular or biocular evaluation was performed. It only appears that the subject was told to place a hand-held 2.2X telescope in front of one eye while performing tasks.

No evaluation by a professional determined if the fellow eye would be suppressed when using the telescope when utilized as needed for mobility.

Post surgically it appears that the subject was left to rehab on his own or on her own or with friends or family members for assistance. I understand from what you reported today that there have been some changes, but in the literature that we've gotten that's some of the questions that I had from that.

In lieu of the potential risk to patients post-surgically I believe that a rehabilitation program should be established.

The patient has to adapt to the magnification of the telescope. When you look through

a telescope, objects are going to appear larger. They're going to appear closer, and move a lot faster.

They have to learn to suppress one eye over the other, and do that consistently when performing their visual concerns.

Mobility in unfamiliar surroundings, different lighting situations, especially near curbs and streets, create a potential trouble spot.

Older patients might take a little longer to learn to adapt to these systems. Older patients possibly are more brittle, and if they bump into things or fall, they could certainly create greater problems than a younger individual.

My understanding is that the telescope is focused for three meters or 10 feet rather than optical infinity. That's fine, because three meters may be a reasonable distance for watching TV and identifying people at a so-called given distance.

However, if a person wants to be able to look through the system at a greater distance than three meters, they would be required to wear a minus concave spectacle lens to see more clearly. When you put this spectacle lens in front of that telescope, you're basically decreasing the magnification of the implant, and therefore, the potential decrease in

visual acuity.

Only those patients with refractive errors of less than six diopters of myopia or four diopters of hyperopia were considered acceptable candidates. What about the patients with astigmatism, and how much astigmatism would rule out a potential patient?

All the patients provided with spectacle correction. Blur created by an uncorrected refractive error would have to be prescribed so as to provide maximum clarity, since any vergence of light through a telescopic system would be amplified by Vergence Amplification.

What is Vergence Amplification? Nothing more than when any divergent or convergent light enters a telescopic system, this divergent or convergent light is amplified or magnified by approximately the magnification of the telescope squared.

So therefore it creates more of a noticeable difference in clarity. When a patient is using the telescope for near, they are required to wear reading spectacles to allow them to focus at different distances. As I said before, the depth of focus of a telemicroscope is certainly more critical than that of a equivalent powered reading lens.

Also if patients or individuals wanted to work at different distances, they would be required to have a number of spectacles that allow them to focus at, say, 12 inches, 10 inches, six inches, which would be a little more critical perhaps than just a simple pair of reading glasses.

In summary, the implantable miniature telescope by Vision Kerophthalmic Technologies may be statistically successful for general vision improvement. I question the benefit of this telescope as it relates to the available magnification ease in solving patients' visual concerns.

It may be used for patients with moderate vision loss, those individuals with 20/70 to 20/140 acuity as I showed in the presentation earlier.

However, what about those individuals where the vision will decrease over time? I do not believe this telescope is beneficial to patients with severe to profound vision loss.

The type of telescope and the appropriate magnification should always be recommended based on the patient's visual concern. It seems to me this was done a little backwards here, and the fact that they just recommended a 2.2 or a 2.7X telescope, and then you went about by asking questions as to how this

telescope was used, and to what benefit the telescope was providing the patient.

The concept of low vision care emphasizes that the person's ability to function visually, and does not entail a numerical classification system. The services are directed at solving problems created for individuals by the impairment of their vision. This was written by Dr. Jose in this textbook.

The FDA requires that any potential research product show effectiveness, and they define effectiveness as a reasonable assurance that a significant portion of the population under uses and conditions of use, when labeled, would provide clinically significant results.

Because of this I truly believe the panel should weigh these concerns carefully when evaluating the effectiveness of the implantable miniature telescope.

Thank you.

DR. MATHERS: Thank you, Dr. Brilliant.

PANEL DISCUSSION OF PMA P050034

Now we're going to move on to the questions that are posed by our FDA, and we will deal with several questions, each as it's presented, and then will be discussed and addressed by our panel

members.

These questions will be projected so that all can see them. And I'll note to the panel members that each of you will be asked to comment on this.

And then I'll summarize.

Would the FDA prefer that I read the question?

MR. CALOGERO: Question one for the panel is: Please discuss the following regarding endothelial cell density: the primary safety endpoint to this study was mean ECD less than or equal to 17 percent. The sponsor reported mean percentage change in ECD from baseline to 12 months of 25.3 percent. Does the panel believe that the study design has provided sufficient data to address the long-term ECD safety issue associated with this device? That's part A. Should I stop here? Okay, that's the first question.

DR. MATHERS: Okay. So this certainly cuts to the big part of the chase here.

The endothelial cell density is a critical issue here. And we have had presentations on both sides.

I know everyone in this panel is not necessarily going to feel expert on this, but you certainly will all have some opinion on this regarding

its overall concern.

I think I'll go around the room. Dr. Palta, would you like to comment on this and your thoughts about this question?

DR. PALTA: Well, one of the problems is that the long term safety, the follow up was not long enough. Like some of the statisticians pointed out.

I personally am also still too unclear about the models. I did not see convincing evidence that one model fit better than the other, and I still have this nagging feeling that perhaps fitting even freely in your pieces exaggerates the trend.

And I think, although additional data would be very useful, I believe that some statistical comparisons of the models might also provide some insight as to how much the decrease really flattens out after two years or three years or whatever the data point was before the extrapolation to four years.

So I would say that of course more data would be ideal, but I do feel that I would have liked to see some more analysis on the existing data.

DR. MATHERS: Dr. Grimmett.

DR. GRIMMETT: I think the panel knows my view on that.

I think I need three things: I need

morphometric endothelial data on the existing photographs. Number two, it would be ideal to redefine what really is the chronic cell loss with a little longer data, another year.

And number three, I'd need in conjunction some ultrasound data on narrow entry or chamber depths, to help better correlate individual cell loss with narrow chambers and actual distances to try to help me analyze that.

DR. MATHERS: Jayne.

DR. BULLIMORE: I think Dr. Bressler as a retinal specialist had the simple but yet clear and concise answer to this one is, if the sponsor defined their endpoint as an ECD less than or equal to 17 percent and they didn't achieve it, then by their own criteria it didn't meet the safety endpoint.

Now we of course, from the comments already made, don't know the final word. Is this indeed safe enough or reasonably safe in terms of what's the chronic endothelial cell loss? Would an individual who had a profound loss of vision perhaps elect to take the chance of needing a corneal transplant because of lost endothelial cells in the hope that they could get better vision? Those are other questions.

But for the simple question, the sponsor did not meet the endpoint that they hoped to meet.

DR. MATHERS: Dr. Heuer.

DR. HEUER: It seems to me whichever model you choose you end up with an awful lot of patients after an expected lifespan well below the 1,000 cell density line.

So to me that points out the concern. What then happens to these patients? What is their prognosis for corneal transplantation? If they have corneal transplantation do they all have to have the lens removed as was done in the two patients that are reported?

Would they be candidates for the new inside-out endothelial transplant approach which doesn't create the big incision that would put their eyes at greater risk for rupture? And as a noncorneal specialist in can only pose these questions; I don't know the answers.

DR. MATHERS: Are you going to pass on this? Okay, I'll keep going in this direction for awhile.

Dr. Huang?

DR. HUANG: I'm thinking the current study has two years data, even though we don't really know

what's the endpoint of the endothelial count is going to be.

But I think maybe it's not just the sponsoring or the industry's responsibility of setting the criteria, because being here a few times, and I look at this question as a recurring problem that every time whenever you have any intraocular implantation device we are going to address this issue over and over again. And what's the endpoint?

Perhaps the industry and FDA probably should work together to define so-called success rate, and what is the acceptable endothelial cell loss rate, and before they set out to do the study.

And after the goal has been or at least the target has been set, then at least we can evaluate the sponsor if a proposal has met the criteria or not.

Now as of this moment, based on Dr. Grimmett's evaluation, the data seem to be somewhat insufficient.

However I still would like to echo Dr. Palta's opinion that we should base on the current data, and maybe we can go back to look at if we have pachymetry data to see if we can make something out of it. Because we have seen patients with 500 endothelial cell count but they still have a very

clear cornea.

So the density itself may not be a total issue.

DR. MATHERS: Dr. Eydelman.

DR. EYDELMAN: Just wanted to comment in light of Dr. Huang's - yes, we have discussed endothelial cell density loss, but I want to make sure the panel was aware, this is the first-of-a-kind device. So while there is discussion of endothelial cell density for phakic IOLs for healthy eyes, this is a whole new ballgame, and therefore, we require your input.

DR. MATHERS: Thank you.

DR. HUANG: Other than the macular degeneration, by definition these eyes are relatively healthy similar to the enrollment criteria of the phakic IOL.

DR. EYDELMAN: Right, but the risk-benefit has to do with macular degeneration.

DR. BURNS: Yes, in terms of the basic question I think they have clearly not, from definition, reached their primary safety endpoint.

But a lot of the discussion depends on sort of extrapolating beyond the data set, and this concerns me for obvious reasons that extrapolation is

risky, though the two models presented to us run out to four years, I'm concerned by Dr. Grimmett's life table expectations that we need to worry about even longer times than that.

So this question of whether we really are going to asymptote or not becomes very critical, and I don't really feel in any position to be confident of either point of view that we've reached an asymptote.

DR. MATHERS: Dr. Bressler.

DR. BRESSLER: So as mentioned earlier there was this cutoff chosen to predict safety, and that was not reached. So I don't think we have sufficient data.

However I do think this is important enough to try to come up with ways to get sufficient data. The sponsors have come up with theories as to how to prevent that initial insult with training, with other meticulous attention to what was going on. But that's a theory. So it may indeed be the reason. And I believe that this would have to get done again with that and show that you don't get that initial insult.

I believe following to the two years is sufficient from the numbers that we have so far. For us in the future to be able to determine an initial approval, and then I believe it would be incumbent

upon all of us to continue follow up on those people who initially came in to see if indeed it does seem to level out at two years, does that stay for three, four, five years, because these people will live 10, 15 years, and you are going to want to collect that data.

So I would say, no, we don't have sufficient data now. It's possible in the future with other studies to I believe get sufficient data to make a safety judgment. I believe two years would still be enough time to see if this happens again or to see if it levels or you need further follow up beyond that.

DR. MATHERS: Dr. Sunness? Dr. Brilliant?

DR. BRILLIANT: I don't have the expertise to answer that question.

DR. MATHERS: Dr. Haik.

DR. HAIK: Just a general comment. I mean I think this is a tremendous need as we all know. Macular degeneration will be epidemic. Twenty percent of Caucasian Americans over 80 will have some form of macular degeneration, and the numbers, as Dr. Bressler pointed out, are just astronomical.

I think that as humanitarians, my God, all of us in Ophthalmology, our goal is to save sight or give sight back, or any of us in vision science and

optometry is to do that, so you want this to succeed so badly. And you want - and you heard these wonderful individuals speak about their personal experience, and that's very moving. It makes you just want to jump on the bandwagon.

But certainly the safety evidence from some very eloquent and intelligent reviewers, both internal to the FDA and outside, and from the industry, sure put enough worries to say, we've got to re-look at the data at least and go farther.

But there's so much hope there, that you hate to throw the baby out with the bath water. But obviously it's not ready to be released in its present form.

DR. MATHERS: And Dr. Szlyk.

DR. SZLYK: Yes. In light of the conflicting data, I think some of the issues can be resolved, and data may be salvaged.

One issue might be to go forward with an increased age requirement for the inclusion for the short term while data are analyzed for the study participants currently enrolled, and that might get control of the issues of age, and also to include those with less shallow interior chamber depths.

DR. MATHERS: I'm not sure I really need to

- oh, I'm sorry, Dr. Ferris. I'm sorry.

DR. FERRIS: So when Dr. Sato did his first radial keratotomy surgery, everybody was enthusiastic about the results, and there was an epidemic of corneal transplantation afterwards. And I know the sponsors as well as all of us are not interested in that, and they've done everything they can, I believe, to make sure that they are carefully looking at this to prevent that from happening.

As most of you know, I like statistics as well as the next person, and I think statistical analyses are helpful, and the past is the best predictor of the future.

But in this particular situation, I don't know what is going to happen, and I think it's somewhat dangerous to extrapolate what I consider short term results to the long term.

I think that there is certainly enough information here to make us concerned about this as a potential problem, even if it's just for a small proportion of the patients it might be a potential problem.

So at the very least I think some longer term follow up to see what the situation is going to be in years three and four would give me much more

solace as to whether lots - whether there should be an unconditional release of this.

And pending that, at the very least, I think it should be conditional, conditional on baseline status.

DR. MATHERS: I think that I will not attempt a summary, because it would just simply be a restatement of most of what they've said.

And what we're telling the FDA should be fairly clear.

I'm sorry.

MS. NIKSCH: I'm Barbara Niksch. I just have a comment on behalf of industry.

As you know when we come to FDA with protocols we obviously set our endpoints up front before the study begins. And during the course of a clinical trial you learn things, just as the sponsor has in this.

I'd just like to request the panel to certainly consider some of the things that the sponsor has already put forward, not only regarding training but perhaps changing the minimum ECD requirement as well, and also looking at minimum ACDs.

So these are things that could perhaps allow this approval process to move forward. And the

sponsor has also agreed to continue to follow the current cohort of patients to collect additional data, and that's also where some of this additional data can come forward to perhaps, you know, change some of the requirements, and perhaps the original improved labeling.

So again just for the panel's consideration.

Thank you.

DR. MATHERS: Thank you.

Let's go on to 1(b).

MR. CALOGERO: Okay, 1(b): Please discuss whether these data can provide a reasonable assurance of the safety of the IMT for proposed indicated population. Please comment on whether any safety concerns regarding loss of ECD can be mitigated by limiting the intended population based on the following: anterior chamber depth; minimum preoperative ECD at entry; age; or other.

DR. MATHERS: This is definitely a related question, and the panel members have given some views partly pertaining to this, so I think I won't go around the table, I will open the discussion. Would one of the panel members like to address one of these on this part (b)? Speak right up.

DR. WEISS: Well, I think if there is indication from or consensus on the panel that there is reasonable efficacy, then certainly we could work with these variables to try to decrease the risk by increasing the anterior chamber depth; increasing the age and the preoperative endothelial cell density to limit the damage that might be done should longer term studies show that this is at a consistent risk as time goes on to the corneal endothelium. So I think you could work with those.

And just a comment with Sate's radial keratotomy which did cause corneal edema. It took 20 years. So we would like to eliminate or decrease that possibility in this case.

DR. MATHERS: Yes.

DR. BRESSLER: I would allow the sponsor to make whatever limitations they want. But I wouldn't make a limitation on any of these yet. Because for all I know, just changing the one variable of the training may allow you to avoid the problems that were mentioned here. So I just want to point out that it's possible that you would learn, if you change a variable that you think is going to make a big difference, that these other do not become a problem, and you'd have to learn that in the next successive

studies.

DR. MATHERS: Malvina.

DR. EYDELMAN: I just want to point out that that implies a whole new trial, a whole follow up.

DR. BRESSLER: I understand, but that's because we're limited without the controls as I mentioned for the efficacy. Unfortunately, because of course, I agree with what Barrett said, we want to help these people that have these scars and loss of vision right now.

DR. MATHERS: Yes.

DR. HUANG: My concern is that at this moment we can change however level we want to put out based on the panel discussion and the industry, but I think most important, we already have some 200 some patients already have this implantation. Perhaps we should do a post trial monitoring, continue to monitor the anterior chamber depth to see whatever their cornea clearance is, if indeed it can be useful for future extrapolation.

Because the pre-op anterior chamber depth may not have anything to do with the future endothelial density, and what matters may be the post-operative anterior chamber depths, or the

postoperative endothelial density has something to do with future corneal decompensation.

So those are the things mainly to take into consideration.

DR. MATHERS: Dr. Palta.

DR. PALTA: This is just a brief question. I'm just wondering if life expectancy is really the criterion that should be used, or some data on a national level on survival of eyesight or eyes rather than total life expectancy. Do you see what I'm saying?

DR. MATHERS: No.

DR. BRESSLER: What I'm saying is, you may outlast your eyes is what I'm saying. You know somebody may survive longer than their vision survives due to other competing eye problems. And I just felt that using the life expectancy as a criterion might be a little too stringent as compared to looking at what other intervening eye diseases may shorten the vision shorter than the life expectancy.

So that's why I felt the age criterion may be a little bit on the stringent side.

DR. MATHERS: Yes, Dr. Haik.

DR. HAIK: I just wanted to comment on the learning curve. I believe I saw that it did not

statistically make any difference. But having been an anterior segment surgeon in the past, and watching that operation, I realize we've got some of the best surgeons in the world doing those procedures now, opening - another kind of difference between cornea surgeons and cataract surgeons, which I didn't fully understand, except that cataract surgeons don't know how to suture any longer, and cornea surgeons do.

But I think you're got an amazing group of people, and I think if you probably made that group even smaller, the numbers of complications would have been less.

So the big worry for me is not whether it can be done by an exceptionally talented group, but whether you can just open it up to the world. And I don't know how you limit learning curves and surgical simulators and things of that sort.

But those things cross my mind when you talk about criteria. And of course we have no way to do that.

DR. MATHERS: Does that address this issue for the FDA sufficiently? Or would you like to have additional input?

Fine, okay. Shall we go on to question two?

MR. CALOGERO: With regard to the long term follow up of eyes, the IMT, performing YAG capsulotomy through the center of the IMT can damage the lenses. The sponsor has proposed needling, or a new method for performing capsulotomy through the periphery of the telescope.

Please discuss whether such management of posterior capsular opacification provides a reasonable assurance of safety for patients with the IMT.

DR. MATHERS: On this particular question I could open up - I could go around again. But I think the expertise of some panel members will differ from others. Perhaps we could hear from those that are most qualified to deal with this particular issue in answer to these questions.

Would someone like to make a comment? The anterior segment surgeons particularly who actually might do this and have a real appreciation for what's at stake.

Yes?

DR. WEISS: There is no reasonable assurance of safety with a YAG capsulotomy, as there is no evidence it's ever been done on a human being. So I don't see how this could be recommended for the population when there is absolutely no human data.

And in fact in the study even the centers elected not to do a YAG capsulotomy, for whatever reasons they did, but they didn't do YAGs. So we can't recommend YAGs, and there is no reasonable assurance of safety.

DR. MATHERS: Yes.

DR. HAIK: I have attempted to do YAGs on keratoprosthesis patients, but through telescopes, and that was not successful either in an animal model or in the human that we tried it on.

So you ended up having to do almost endoscopic or some sort of vitreous procedure to be able to take it out.

DR. MATHERS: Yes, that wasn't noted, but of course, a pars plana vitrectomy approach can peel off a membrane in the posterior segment.

DR. HAIK: And with most of the keratoprosthesis we ended up having to do that, almost always it would get a big thick dense secondary membrane that would sling the telescope forward if you hadn't done a good anterior tractomy.

DR. MATHERS: And we haven't really addressed the question of needling. I gather that no one really remembers how to needle.

But it may not be the approach - the way

to solve this problem particularly, and I think the panel, it looks like, doesn't wish to really add much data to your concept of needling to get rid of this problem.

DR. HAIK: I've needled before, but it was when you had a chance to see, either at the slit-lamp, or somebody is at the microscope, and you can see what's going on behind you. I've never seen a patient with one of these lenses and I have no idea whether I would feel good about controlling the needle, whether it would scratch the posterior part of the optic, whether I would dislodge the lens.

I just have no clue as to how well anchored all of that is in there.

DR. MATHERS: Does the panel have a feeling about how important the posterior capsule is going to be?

Dr. Ferris.

DR. FERRIS: As a medical retina person I feel totally confident to answer this, but of all the concerns I have, given the ingenuity of ophthalmologists in this country, I'm sure they would figure out a way, even if that got to be a problem, whether it's coming from a pars plana, getting new knitting needles, or whatever, that they will figure

out how to get rid of the capsule.

So of all the things that I'm concerned about, this one is pretty low on my list.

DR. MATHERS: Thank you.

Let's go on to question three. Oh, I'm sorry, 2(b), or was it -

MR. CALOGERO: Please discuss your concerns if any regarding posterior segment examination and treatment of eyes with the IMT.

DR. MATHERS: Now we can hear from Dr. Ferris' level of expertise.

DR. FERRIS: Now I do have something to say.

DR. MATHERS: You have the floor.

DR. FERRIS: Well, I am concerned about that. Because although it's clearly possible to visualize the posterior segment, there are two issues that I'm concerned about.

One is, in an age-related eye disease study, roughly a third of the patients that had geographic atrophy developed choroidal neovascularization, so it is not like these patients are not at risk for developing choroidal neovascularization.

Now there may be an acute phase, and if we

take these later patients, the rate I'm sure is less than a third in this group. But it's still a concern, and I'm concerned I don't know whether you can do OCT on these patients.

I do know, not just from what I saw today, but also talking to some people, that the view that you get, and your ability to do angiography is limited by this device. So it will make treatment harder.

There is another concern that isn't directly there but is a concern to me as an epidemiologist. And that is the five-year rate of retinal detachment is roughly one percent in the extracapsular group. As I remember things in the intracapsular days, the rates were higher.

So these patients are at risk for a problem that is going to be despite what I just said about how inventive our surgeons are, it is going to be very difficult to approach the retinal detachment in these patients, and that is a real concern.

And in fact I think given those rates, it's fortunate that we haven't seen one in these 200.

DR. MATHERS: Dr. Bressler.

DR. BRESSLER: So I agree with what Rick said, for the people with geographic atrophy that would get this, we would probably need to know if we

can identify the development of choroidal neovascularization, and reliably follow it.

In addition, we will have a population of people over the next several years that have received treatment let's say with ranibizumab and have stabilized, and hopefully don't need injections indefinitely, but maybe after some point in time would stop needing treatment.

That could go on for six months, then someone may get an implant if they were not able to stop the vision loss, and so it was already 20/100 or 20/160. But then we don't know that all those treated eyes may not eventually begin to develop neovascularization with leakage again, and we don't know how that would be identified.

So it's not just the geographic atrophy cases that may develop neovascularization, but the cases that are actually treated at a level where unfortunately they still might have lost central vision but benefit, then you need to follow them to pick up whether you need to treat them later on.

And that does require a good view, good fluorescein, and some people or many people at this time, their standard care is to also use OCT to follow.

So we need that information. It may be easy to do; we just don't have that information.

DR. MATHERS: Any further comments on that question?

The chair feels that this is a significant issue, that the issue of being able to treat and evaluate these patients after they have a lens may not be as evident now, but this is a very, very rapidly changing field, and it's most likely that new treatment modalities and need for treatment assessment will not away; it will increase, so that limitations on future treatment might be a significant issue, probably will be, in my opinion.

Is that sufficient on that question? Yes?

DR. HAIK: I guess, would you add diabetes then as an exclusion factor?

DR. MATHERS: That could be a suggestion.

MR. CALOGERO: Question three: the proposed safety and effectiveness criteria for visual acuity is based on unadjusted preoperative acuity rather than acuity predicted from the magnified postoperative retinal image. A, please discuss where the unadjusted preoperative acuity baseline is adequate for evaluation of safety and efficacy of this device, and maybe I'll read B also, it's related:

Please provide any recommendations on what additional analyses are needed if any to evaluate visual acuity measures of safety and effectiveness.

DR. MATHERS: This of course brings in the issue of assessing the issues of cataract and other problems.

Could we hear from Dr. Ferris?

DR. FERRIS: This is the other area that I have the most concern, and I agree completely with what Neil said earlier.

I don't know whether not having controls fatally flaws this study, but it certainly damages it to a great degree. Because I don't know what a similar group of patients who had cataract - apparently these patients had some degree of cataract which is unknown and maybe unknowable, given the ability to grade cataracts, but if there was a comparable control group, especially if there was a randomized control group, then we would have some ability to say to what degree this is effective compared with the normal approach.

And as Neil said, without that control group you're left guessing as to what might be true.

And I take Mark Bullimore's point that he made earlier that interestingly at least in the lower

powered device the amount of improvement that was seen with a telescope was equal to that that was achieved after the surgery suggesting I guess that the lens opacities were not particularly severe.

But we're left guessing, and that's a very uncomfortable place for me to be. So I personally think at some point they need some kind of appropriate control group if they're going to get - at least for me. If I'm going to balance efficacy with safety, I've got a number of safety concerns and I don't have a good measure of efficacy, I'm left in a very uncomfortable place.

DR. MATHERS: Yes, Dr. Burns.

DR. BURNS: Yes, I want to second that opinion. And I had two things I noted in the data that sort of raised the issue for me.

One is the fact that only 18 percent, 19 percent of the patients with the hand-held telescope got a large effect, and when the implantation was done they had a higher increase in acuity.

But the flip side of that is, almost 20 percent of patients had more than the expected increase in acuity. And both of these suggest to me that there is a large cataract component in the improvement that might slide that whole scale

downwards.

So I do believe something better should be done for assessing the cataract, even if it's getting the best possible acuity ahead of time through a telescope that's matched, externally.

DR. MATHERS: Dr. Sunness.

DR. SUNNESS: Thank you. I have a few considerations that really have not been touched yet.

But first I want to say that the sponsors are really pioneers in this area, because as will certainly become clear in our discussion, there really are not good standards currently for how should you do rehabilitation, how do you assess outcomes, how do you look at geographic atrophy or similar diseases over time.

So I really think that what they've done is very important, even if it's going to have to be refined in the future.

I was privileged to direct a long-term natural history study of geographic atrophy at Wilmer from 1992 to 2000. And one of the things we published a few years ago is that when you looked at patients who had bilateral geographic atrophy, over a three-year period, 17 percent of them gained two or more lines in the fellow eye - I'm sorry, gained two or

more lines in the worst-seeing eye at two years. This was without - there was no formal rehabilitation training done, so they spontaneously gained two or more lines in their worst-seeing eye.

And we had done scanning laser ophthalmoscope analysis of their fixation patterns at the beginning, and subsequently. And these patients initially were not able to take what they wanted to see and put it on the part of the retina that was seeing, whereas three years later they were able to do this; they could put what they wanted to see on whatever you want to call it, a PRL, an eccentric locus of fixation. But the point is, it was on a part of the retina that was seeing.

And these patients obviously did not improve clinically. Geographic atrophy does not go away. The improvement was basically the fact that they adapted better to how they can use their vision.

So the criteria for choosing the eye to operate on in this study forced it to be the worst eye if either eye was better than 20/200, and it was a choice of the patient and the doctor if both eyes were 20/200 or worse.

So one would presume then that most patients chose the worst eye for the implantation of

the device, so this really comes into - one has to take this into account. In other words, is this a better use of eccentric fixation where initially the patient sort of ignored the worst-seeing eye, and used the better eye optimally, and now they're improving the ability to use that eye.

And to me that also addresses the issue of why didn't the visual acuity improve more in patients who had good baseline visual acuity. I would expect with the telescope a patient who has 20/80 visual acuity would more likely have a smaller scotoma, and would actually be able to get the full benefit of the telescope. And yet they did not. The people who improved the most were the people who had more severe visual acuity loss.

So to me that either says that in fact part of the improvement was related to this issue of moving your fixation to an eccentric fixation, or that really what we're looking at is the people who had more severe vision loss had worse cataracts, and maybe when the cataracts were removed they saw better.

The other thing I was wondering is, whether there was a change in visual acuity after the short little telescope trial, a small amounts of changing, and which visual acuity was actually used at

the baseline.

Because one could argue that maybe the way to approach this type of case is to do an initial certain amount of rehabilitation training, and then test the visual acuity at that point and consider that your preoperative visual acuity.

And then I'm not going to be much longer, I think it was important to stratify the data therefore by whether the operated eye was the better or the worse eye. And in particular I really think that the data is already there to at least try to approach the issue of controls. Because the patients in this study had to have bilateral macular degeneration and vision loss. And the sponsor has presented nothing in terms of what happened to the fellow eye.

So it would seem to me that at some level at least what happened at the fellow eye would be a type of control that could be used to compare to what happened to the operated eye.

It's not perfect. Those eyes did not specifically undergo cataract extraction. But at least you would know what's going on, and if you for example did the rehabilitation training involving both eyes, then you would be able to sort of factor out the

rehabilitation training as the issue.

So just to summarize, I think the initial analyses that are needed are, first of all, stratification of the results by whether the eye implanted was the better or worse eye at baseline; look at whether there was improvement preoperatively by the short amounts of rehabilitation training that was done; and incorporate some evaluation of the visual acuity change in the unoperated eye over time.

Thank you.

DR. MATHERS: Yes.

DR. EDRINGTON: The other factor on the baseline, I don't know what attempts were made in terms of the refraction that was used for the baseline visual acuity, or the current correction, and how current their correction was.

DR. MATHERS: Yes.

DR. BRESSLER: Neil Bressler. My only comment is, we don't have, I believe, a good idea of what this magnified adjusted vision would be, or what it all means.

So I would still suggest you go with the adjusted preoperative acuity as they have done.

As a secondary outcome you want to see that it's consistent with the magnification contrived

so to speak image. But I like knowing what was the best vision they had beforehand, and now that they put this in, what's the best vision they get afterwards. I believe it takes everything into totality but still gets the other one as a secondary.

DR. MATHERS: Dr. Huang.

DR. HUANG: I echo Dr. Bressler's comment. As an anterior segment surgeon, we do sometimes operate on the high myopia patient, and then you know, at various FDA trials that we also evaluate on the LASIK, on the high myopia patient, and then we didn't set up different criteria for reviewing those subgroup of the high myopia patient that we modified their postoperative outcome based on the amount of correction.

So as a result we see patients from 20/20 minus 10 to become 20/15. So there is definitely a magnification factor involved in terms of changing the refraction. But if every study were to change to different criteria, then it would make all the studies very confusing.

DR. MATHERS: Dr. Grimmett?

DR. GRIMMETT: Michael Grimmett. I don't think that the baseline should be adjusted, so I wouldn't do the magnification adjustment for the

following reasons.

By way of history for corneal refractive procedures we were in the habit of subtracting out the magnification basically to unmask losses of best corrected vision. We were trying to see if the magnification hid irregular astigmatism; that was the reason. So there was one particular item we were going after.

With this device, in contradistinction, there is not one thing. If we have increased magnification, which should increase your vision, we have decreased luminance, if I've read the slides correctly, I'm not a vision scientist, .9 LogMARs, 10 percent transmission, to a 90 percent reduction in light. That should reduce vision, competing against the magnification in a macular degeneration patient that is; it probably wouldn't hurt a normal.

Number three; we have the removal of a cataract, which should improve vision.

And number four, we have whatever optical aberrations are induced by the device itself, if they're not refracted correctly, the vergence amplification that Dr. Brilliant talked about.

So subtracting out the magnification in my mind doesn't unmask one thing. I'm still left with

three other competing factors. I can't sort it out.

My advice would be, not to subtract the magnification. Go with whatever improvement you were expecting. After all, the device is supposed to give magnification. We're not trying to evaluate cataract surgery with a telescope, subtracting magnification.

DR. BRESSLER: Neil Bressler. I just want to confirm, we weren't at odds. That was our opinion. Because when you started it sounded like I disagree. Okay, we were in the same part.

DR. GRIMMETT: I agree with Dr. Bressler.

(Laughter)

DR. HEUER: Clearly way outside my area of expertise, but I would argue against trying to use the fellow eye as a control.

I think in this situation we put a magnified image in the one eye, so you've taken away any stimulus to learn eccentric fixation in the other eye. So I don't think it's going to begin to do what you expect it to do. At least I think it would be a potentially flawed control.

DR. SUNNESS: I agree with what you're saying. I mean it's not perfect, and it's not a control.

But for example one would want to know if

the worse eye were chosen as the eye that got implanted, with that telescope is it now the better eye for reading, leaving the patients to themselves. Do they prefer one eye? And in fact which eye works better? We don't have that information either.

DR. EYDELMAN: Just to step back to Dr. Huang's comment, I just wanted to clarify that when we evaluate refractive lasers for high degree of correction, we do adjust minification or magnification for the efficacy of the procedure. So in that regard this is not a new question. But it is obviously a much more multifactorial analysis in this case.

DR. MATHERS: Thank you.

DR. FERRIS: Just with regard to controls, as far as I'm concerned there's really only one adequate control group, and that's a randomized comparison. A poor distant second might be an observational group, a concurrent cohort, the fellow, this is a patient issue I think as much as an eye issue. So I think it would be not very good as a control.

DR. MATHERS: And the chair agrees with Dr. Ferris on that issue, that randomized control is the gold standard.

Yes.

DR. WEISS: Well, just bringing it back down a few notches, we know what the gold standard is, but if one wanted to try to glean more data from this, and not to use the word control, but if perhaps fellow eyes in some of the patients had also undergone cataract surgery, had also had implantation of an IOL, one might glean a little bit of data to see how those eyes fared by comparison to the eye that had this implant.

DR. MATHERS: True.

DR. BRESSLER: Neil Bressler. The problem is that with neovascular MD, which is often bilateral, the outcomes are often not symmetrical, and so you have a very, very, very weak control.

DR. SUNNESS: I'm sorry I used the term, control, because as you say - I didn't mean it that way. I meant it as a comparison and giving some extra information.

DR. MATHERS: Okay, all right.

I think we ought to go onto another issue, unless you particularly want us to knock this about more.

MR. CALOGERO: Panel question: In the IMT trial the rehabilitation program was implemented by the subject with assistance from the family.

Professional orientation, mobility and reading instruction were not provided. No validated methods of measuring the outcomes of training were utilized in this study. A, please discuss whether you believe that the functional safety and effectiveness of the IMT has been adequately addressed with the vision rehabilitation program and the quality of life questionnaires used in this study.

And then related, B, if not, please discuss modifications to the vision rehabilitation program recommended for patients that receive the IMT.

DR. MATHERS: Some of our panel are much more experienced with visual rehabilitation and training issues than others; I am not.

Do we have comments from those who have a particular interest in this? Or anyone else?

Why don't you speak? Dr. Szlyk.

DR. SZLYK: Well, I think that vision rehabilitation training has been demonstrated by my lab and others to show considerable improvement in functioning with external telescopes, and I think the issues here of multiplexing are much more complex, and perceptual adaptation would be much more difficult with the internal telescope, so vision training would be critical with this condition.

So I think a curriculum needs to be designed, and I think they had a platform that was presented by the sponsor that had been developed by Eli Pelli, and that can be taken and utilized.

And I agree with the recommendation that it should be a requirement for labeling, vision rehabilitation with these patients became of these issues.

DR. MATHERS: Dr. Sunness, or I'm sorry, Dr. Burns, would you agree?

DR. BURNS: I certainly agree with that, and I'd like to add the fact that I think there should be pre and post rehab to evaluate the potential of the person being binocular and learning to use one eye or the other to suppress one eye or the other, and to be taught appropriately how to use the device afterwards for safety reasons.

DR. MATHERS: Dr. Bressler.

DR. BRESSLER: Neil Bressler. I respect our experts in this area, which is not my area. But from the outside looking in, I worry about requiring a program if I'm not certain or reasonably certain that it's going to help them.

So maybe you are reasonably certain that it's going to help them, but boy, it'd be interesting

if we found after this device is used, and you randomly assigned people again to doing the rehab program or not, to somehow show that those who did the rehab program did better, then I'm ready to require it.

But before it, maybe I'm ready to strongly recommend it or something.

DR. SUNNESS: I think one of the problems - this is Janet Sunness - is that it's exceedingly difficult to say this is what we should do when low vision rehab is not at that stage yet.

In other words if you told each of us what should be the vision rehab program for these patients, we probably each would have a different idea.

Having said that, though, we have to start where we're starting, and I agree with Dr. Brilliant that I think there should be a pre-op and a post-op rehab component.

Part of it, as I mentioned before, would be to see what percentage of the improvement is just by rehab itself, and then you go on and have the treatment and see what that does.

So while I agree that they should have rehab, I think this is going to be an increasing problem in general in the future. I don't know what I

would say they should have.

DR. MATHERS: Yes. Malvina.

DR. EYDELMAN: I just wanted to point out that even though we don't know what was the density and frequency of dense nuclear cataracts or any other kind of cataracts, this is indicated for patients with cataracts.

So I just want to make sure that when we're discussing pre-op rehabilitation, the panel gives me guidance as to how dense a cataract is still applicable to training.

DR. SUNNESS: I think any amount, because you don't know - it's a little bit difficult problem if you have someone who has macular degeneration and a cataract, how do you parse out what's the macular degeneration and what's the cataract. But presumably, the rehab training will first of all allow the patient to learn how to move their scotoma out of the area of interest, and secondly, you want them to use low vision devices that will improve their vision in whatever their situation and whatever the cost.

DR. MATHERS: Dr. Burns?

DR. BURNS: Yeah, this may be obvious to the specialists, but I want to touch on something Dr. Szlyk mentioned, and that is, a critical part of the

logic of this device is the ability to use one eye for wide field and one eye for magnified vision.

So part of any such program really has to both assess preferably assess patients' ability to do this beforehand, but definitely make sure that's happening afterwards.

DR. MATHERS: I'm sorry, we haven't heard from Mr. Bunner. Would you like to address?

MR. BUNNER: Thank you, Rick Bunner.

Just sort of flipping the issue, I know the availability of professional low vision services vary from state to state, and that would be obviously an issue.

But when I look at it from a consumer standpoint, so if we're not going to label requiring this service, what's the alternative? And the alternative that was done in the study was patient and family-centered rehabilitation responsibility.

And to me that's an even greater variability. So it seems like it makes more sense, if you have to pick the lesser of two evils, or the better outcome for the patient, that if the person is going to commit to this kind of surgery, that one of the steps of that would then also be professional rehabilitative services rather than putting that onus

on the family.

DR. MATHERS: One more comment. Well, Malvina?

DR. EYDELMAN: I believe Dr. Lepri has a comment.

DR. LEPRI: Thank you.

I wanted to clarify for the panel members that FDA's concerns about requiring rehabilitation was not for the entire rehabilitation program, which by the way, what the sponsor laid out in terms of visual exercises and practice sessions was excellent.

Our concern was about orientation and mobility training after surgery because of putting the magnification in the patient's eye, their ability to negotiate steps, curbs, shadows and all those other types of things poses a potential safety issue in the elderly population.

The remainder of the rehabilitation program should be recommended, not necessarily required, based on the patient's visual needs and demands and concerns about what they want to be able to do.

Thank you.

DR. MATHERS: Did you want to say something else?

DR. BRESSLER: I apologize, but just to address the question directly, if we believe that the functional safety and effectiveness of this has been addressed by the vision rehab program, I would say no because we didn't have specific questions asking about orientation and mobility to the people. That could still be asked later on, so I recommend that they get those questions in.

And number two, the NEI-VFQ is validated, and so I don't think it addresses the safety and effectiveness. Because for all we know their NEI-VFQ is worse than if they just had the cataract surgery alone to go to that question.

And then I still hope you will get back from the sponsor the validity of the ADL.

DR. MATHERS: Okay, let's move on to another question. Thank you.

MR. CALOGERO: Panel question five: Regarding the rehabilitation training program, to teach IMT subjects to use their implanted eyes for essential vision tasks and their fellow eyes for peripheral vision tasks, there are two questions.

The sponsors provided no direct performance measures showing that subjects can learn to shift binocular suppression from one eye to the

other at will. Please discuss where the available evidence provides reasonable assurance that IMT subjects can safely and effectively use their IMT eye for central vision and their fellow eye for peripheral vision.

And then B, please provide any recommendations you may have for modifying the instructions for dealing with binocular rivalry and suppression problems.

DR. MATHERS: Okay. Dr. Ferris.

DR. FERRIS: So I'm sure the answer is, some can and some can't, and I think that was the whole point of the discussion we just had that some attempt early on to sort out those that are going to be able to deal with this kind of suppression or whatever it is, and like this kind of device, and those who don't, before it's in your eye and it's harder to undo.

So I think informed patient decision is the answer here, and the best it seems to me, I'll turn to the people that do this all the time, but it seems to me that practicing with external devices and so on would be a good way to try to sort out those that are good candidates and those that aren't, and I believe that's what the sponsor did.

DR. MATHERS: Janet.

DR. SUNNESS: I think there are certainly some ways to approach this. For example, let's say you measured your near acuity and a measure of reading rate for each eye independently, and then measured what the two eyes do when they're together, and compare that with your findings, you would know first of all whether they're using the implanted eye, and secondly, whether their binocular or biocular use of it is interfering with their ability to read, as contrasted with covering one eye.

So I think that there are ways to approach this, and again it involves making the fellow eye more of a component in the studies that are done.

DR. MATHERS: Yes, Dr. Szlyk.

DR. SZLYK: Just one comment about the three-day trial period. Having more of a monitoring of the patients' use of the external telescope during that three day, and I thought the three days is much too short for a patient to adapt to the use of a telescope. Maybe having follow up phone calls from a low vision professional to ask if they are using the device, and what they are using it for, over a longer period, say two weeks, and then coming back and having some outcome measures, being tested for reading and

distance vision, actual activities on it, with the use of the external telescope.

But more adaptation to the external telescope, practice multiplexing.

DR. MATHERS: And the chair believes that this is probably more complex than the simple peripheral central vision evaluation, in that the brain will pick up data wherever it can, and that there are a very wide range of abilities to do this, we see in refractive surgery. So I don't think these patients are going to fall into a neat I use my central vision here, I use my peripheral vision there. It's going to be much more complex, and predicting it is going to be somewhat difficult over a short period of time.

Is that sufficient on that question? Yes.

DR. PALTA: Well, I kind of thought that the activities of daily living may, at least indirectly, may be addressing that point, if they improve certain functional aspects, it seems that some coordination must be going on there.

DR. MATHERS: Yes, Dr. Brilliant.

DR. BRILLIANT: I've seen often where individuals have two eyes that are not equal in acuity, and therefore, will have some type of double

vision, or diplopia. And when we ask them to read, and we ask them to read binocularly, they just close - they inadvertently close - they physically close one eye.

So we don't know if those were the results here when they're using - I assume - the telescope for reading with a reading lens, they just basically closing that eye. Because it would seem to me almost impossible to read with one eye magnified to that extent and the other eye not, with such an acuity difference, to be able to read comfortably and get accurate reading acuities.

DR. MATHERS: Okay.

MR. CALOGERO: Okay, this is the final question, number six. This is a rather long question.

The sponsor proposed the following indication of the IMT: the IMT implant is indicated for use in adult patients with bilateral stable moderate to profound central vision impairment due to macular degeneration. Patients selected for implantation should meet the following criteria: 55 years of age or older; bilateral stable central vision disorders resulting from age-related macular degeneration as determined by fluorescein angiography and evidence of cataract; distance BCVA from 20/80 to

20/200, and adequate peripheral vision in one eye, the non-targeted eye, to allow for orientation and mobility; achieve at least a five-letter improvement on the ATDRS chart in the eye scheduled for surgery using an external telescope; show interest in participating in a postoperative rehabilitation program.

That's the current criteria. Please discuss whether you believe that the data presented in the PMA support reasonable assurance of safety and efficacy of the IMT for the proposed indication. And then if not, please comment on whether your concerns can be mitigated by modification of the following: age; preoperative VA; definition of minimal acceptable peripheral vision; type of AMD; or other.

DR. MATHERS: Let's break this down a little bit, because we've been knocking on some of these doors already.

Would someone care to comment on this device regarding the suitability of a higher age cutoff or at least summarize the group's feeling on that?

DR. WEISS: Well, with the question there is somewhat of a consensus about concerns about not only efficacy but also safety. I think the only way

this can be rescued is to increase the age.

So I think the way the panel's discussions have been going, if this got an age 55 - if age 55 got considered, we would have to have an exceedingly high endothelial cell count because of the - which would be unrealistic because of the concern long term about endothelial cell loss.

But if we brought this up into a much higher age category, which has been brought up by other panel members, but I would concur, there might be the possibility of having limited risk exposure for the elderly population.

DR. MATHERS: Does anyone have a different opinion? Or is that how the panel feels generally?

Yes.

DR. HAIK: Barrett Haik. I'm not sure how much plasticity you lose as you age, and some of the patients, although I know macular degeneration is totally isolated, if I see a 90-year-old with severe macular degeneration, usually they are not going to adapt well to anything I do for them in terms of magnification, as somebody 55 would. I don't know whether that's just related to concomitant factors or just loss of plasticity.

I mean every once in awhile you see

somebody who shows remarkable recovery following something you think is irreversible, and you don't know how that happens, and other times you expect people to recover.

I don't know, I think the older we lock him in, the less likely they are to be successful.

DR. MATHERS: Right, certainly going up in age decreases the endothelial issue, but it brings into question other issues that are perhaps equally relevant.

DR. BRESSLER: Neil Bressler. I just wanted to clarify to understand, is this greater age to expect that people will have a shorter time for the endothelial cells? Because I'm thinking a 55-year-old might pass away at 65, and so that person had 10 years, and that 85-year-old might live to 100, and so statistically yes, but I'm worried about the individuals, you can't predict that as they're entering the trial.

So if you're trying to avoid like a 15-year lifespan, I can't predict that from the person walking in. So that's why I'm not sure I can mitigate it with age.

DR. SUNNESS: I definitely agree. I can't predict lifespan either.

DR. MATHERS: However, predicted endothelial failure, certainly at a relatively short duration of, say, 10 years in a very high percent - in 10 years a very high percent of these are going to fail. That's not a very long time. And that's why if you're really going to move it up to a time when that is going to be effective, you're going to get into a very old age population.

DR. BRESSLER: Neil Bressler. Exactly my point. You might be just saying 90-year-olds.

DR. MATHERS: Yes.

DR. FERRIS: Rick Ferris. So 90 years is extreme, but Janet might be able to tell us what the average age of her patients with this degree of geographic atrophy was, and actually I think the bulk of these patients may be in the 75 plus age group, and certainly when intraocular lenses were first initiated, there was this concept of reducing your overall risk by limiting who was going to get them until we had some longer information. And that risk reduction strategy seems like a pretty reasonable plan to me.

DR. MATHERS: Yes.

DR. SUNNESS: Janet Sunness. The media age of our patients was, I think it was about 78, and

that's all comers, not just people who had had visual acuity loss to that level.

And the other thing is that there's very limited information about the 90-plus age group, but the two studies that have been done suggest that 22 to 35 percent of people aged 90 or over have geographic atrophy, as compared with 3-1/2 percent if you look at the whole group 75 and above.

So in fact if the population is going to age and live longer, you're going to have a lot of 90-year-olds.

DR. MATHERS: And I will remind us all that these life tables are current data, but that the statins have completely rewritten the life expectancy map. We're increasing it one year per decade at the present time, and that may accelerate a lot in the next decade.

So life expectancy is an unknown here, and could be a lot longer than we're anticipating.

Okay, let's go down to preoperative visual acuity. I think this will be a little less contentious, maybe.

Does anybody have a thought about preoperative visual acuity as being a limiting factor, or should it be an important consideration here?

DR. FERRIS: This is Rick Ferris. Again, I'd like to ask Janet. But it seems to me that the interesting part about the geographic atrophy in the better end, the 20/80 the 20/100 is, they're probably also the highest risk group for decreasing in the next several years. And I wondered, actually the sponsor may even have some data with regard to change over time, but that may have been one of the competing risks for why they apparently didn't do as well as you might have thought they were going to do. Because they've got their worsening disease at the same time you've given them some help.

So to me the - at this point, the worse eyes or some lower degree of preoperative vision may be appropriate, for several reasons.

DR. MATHERS: Yes, Dr. Sunness.

DR. SUNNESS: In our population the overall rate of three line visual acuity at two years was 30 percent. For those patients who had visual acuity 20/50 or better it was 40 percent; for people in the 20/50 to 20/200 range it was about 15 percent over the two-year period.

The other issue with people at the lower range of acuity is that you probably have a fair number of them who actually have a very limited

central spared area surrounded by geographic atrophy. So in other words they don't have that big an area to use. They might get to 20/80 if you go by single letters, but if you ask them to read words, or to recognize people, they don't even do that well, because they're only seeing a piece of it.

And in patients who then have magnification by whatever means, even less is fitting into the spared area. So that is still another thing that could affect the improvement for the better visual acuity level.

So I think it's sort of a balancing act. On the one hand the people with worse acuity actually got more improvement; on the other hand, the people with better acuity are more likely, as Dr. Brilliant said, to move into the 20/40 or 20/50 range with this device although they didn't seem to do that as often as we'd expect in this study.

DR. MATHERS: Yes.

DR. HEUER: Dale Heuer. I actually need some help from the people gifted in vision rehab to address what I heard Dr. Brilliant say is that in fact maybe we need to limit this on the other end; that the folks beyond 20/160, I forget what the cutoff was, may not be getting enough magnification from these devices

to be meaningful.

I need some help.

DR. MATHERS: We seem to have conflicting information.

Yes, Dr. Brilliant.

DR. BRILLIANT: We know magnification improves visual acuity pretty much by the magnification itself. So if a person's acuity is 20/800 and you improve acuity to 20/400, or 20/300, from a functional point of view, what is 20/300 going to do?

And I guess, and again I'm not a glaucoma specialist, but I sort of look at as, there is a new magic drug that is being reported on now that drops acuity 15 millimeters of pressure on the average, and we find that those individuals with pressures of 50 or higher get an even better result; maybe drops it down to 20. And we say this drug could be used by itself.

Is that an acceptable drug for an individual who has 50 millimeters of pressure? We dropped it down to, say, 30 millimeters of pressure.

Statistically we show that it's a pretty dramatic improvement, but is it really doing the job?

And so I say the same thing when it comes to low vision acuity, and functional acuity. There is

no doubt that a telescope will improve visual acuity, on an individual with worse acuity than perhaps 20/100 or 20/140 or whatever we want to cut off, we require more magnification than 2.2 or 2.7X to allow that person to be functional to do some of the tasks that we want to do as an individual with reduced vision.

That's basically what I'm saying.

DR. MATHERS: Okay. Jayne.

DR. WEISS: Well, I wonder if we get into personal judgment here more than science or medicine. Of course you have a certain goal, but what do you do in that low vision patient who will never reach that goal? We have nothing for that patient perhaps, and you can correct me, because this is what you do for a living, and this is not what I do for a living, but if there is not, in the absence of an ideal goal, maybe better would be satisfactory to that patient.

And I would really wonder, in terms of stratifying the results that were done in this trial, to look at those patients who had more severe visual loss and to see if we had anything in the data what their satisfaction level was. Was there satisfaction even though they didn't reach those benchmarks of 20/40 or 20/50? Did they still have a high satisfaction level? If such data is available.

Because if they did, then I don't think we should be paternalistic or maternalistic and judge for an individual patient what's good enough.

And again I don't do this for a living. I'm a refractive corneal surgeon, so you deal with these patients, and perhaps I'm a little too idealistic in terms of my viewpoint.

DR. BRILLIANT: Basically what I'm saying is, I have no right to determine whether a person with 20/800 who improves to 20/400 to say that that is not good enough. It's really the individual that would have to say that.

All I'm basically saying is, we only have two magnifications available to us with this implant: 2.2 and 2.7. So for those individuals with 20/800 acuity, I think they should be shown the option of getting that 2.7 as perhaps an external telescope to see if that's sufficient acuity to meet their needs or if perhaps a five or a six or a seven or an eight X telescope, which would improve acuity even more, and certain disadvantages as well, but improve acuity enough to allow them to do more things perhaps. And that's what I'm saying.

DR. WEISS: But I would hope that they would do that for all patients, even the moderate

visual loss ones. To give them the choice of an externally held device, versus this invasive surgery.

DR. BRILLIANT: Right, but I have not seen that in this presentation, where a person is shown anything else other than 2.2X external telescope, and I was not clear as to whether a person's visual concerns were addressed prior to implanting the telescope.

DR. MATHERS: I don't think we're getting much consensus.

Do you have a brief comment, Dr. Ferris?

DR. FERRIS: Well, I have a suggestion, and that is I think all A, B and C there are part of appropriate informed consent and pretreatment evaluation, and that picking something that we can't pick that's an individual decision that is based on individual desires, and the Admiral Farraguts of this world are going to want to do this no matter what, and the Hamlets are not going to want to do it. And I don't think we're in a position to tell them what to do.

I think we might be in a position - well, I wish we were in a position to be able to tell them what the risks were. We can give them some idea of what the benefits are. So I don't know how they can

make the decision. I would have a hard time making the decision right now, but I think all three of those fit in that mode, that you need to give them the data that are available, and let them make the choice after they've practiced with these various devices to decide whether they like them or not.

DR. MATHERS: Malvina.

DR. EYDELMAN: In light of the discussion I just wanted to make clarification.

It is my understanding that during this trial people with very low vision were not given an option of a telescope with a very high magnification. So therefore looking at the satisfaction data from this trial is not really reflective of patient's ability to compare the options.

DR. MATHERS: Thank you.

Would you like clarification - would you like information on AMD? Shall we go around that? Would you like that?

Okay, does someone have some thoughts about particular types of - yes.

DR. SUNNESS: Again, as Neil mentioned before, it's very hard to predict first of all when choroidal neovascularization is going to reactivate. But in particular in my study we had patients who had

geographic atrophy with no evidence of choroidal neovascularization in one eye, who had choroidal neovascularization in the other eye. And they had an 18 percent rate of getting choroidal neovascularization at two years, and about a 34 percent rate at four years.

So it's a significant rate. By comparison the bilateral geographic atrophy group had a two percent rate at two years, and 11 percent at four years.

So that's something to take into account.

DR. MATHERS: So by that, the bilateral geographic atrophy would be the least problematic, because the choroidal would be an issue.

Someone else have a conflicting opinion? I think that that sounds reasonable.

Okay, I think we have gone over the - yes.

DR. EYDELMAN: C.

DR. MATHERS: Well, I was hoping to have included that, but we can talk about peripheral vision. Would someone like to comment about the nature of peripheral vision in this case?

DR. EYDELMAN: Let me just give you a little clarification. This has to do with how the indication is worded, and whether you felt that more

specific, a more clear definition of acceptable, quote unquote, is needed.

DR. MATHERS: Do we think that peripheral vision should be a significant issue in the patient's selection.

Okay, does someone have an opinion about that? Anyone on this side of the room?

I don't actually. I think it should be left to the discretion of - yes.

DR. SUNNESS: Janet Sunness. I think it's also difficult to assess even peripheral vision in people who have central visual loss, because a visual field assumes that a person has stable fixation and central fixation, neither of which will necessarily be operants of this case.

So I agree basically that I think it would be difficult to impose a particular type of visual field. But on the other hand some general feeling that the person has at least I would say like 30 degrees in each quadrant should be measured.

DR. MATHERS: Dr. Szlyk.

DR. SZLYK: I would think they would need a reasonable amount, I agree with Dr. Sunness, to be able to see to the side of the telescope, since mobility is a major issue with this group.

DR. MATHERS: Dr. Brilliant.

DR. BRILLIANT: I think that you could certainly devise tests which would be very easy to evaluate a person's ability to get around, and the obvious thing would be to cover up one eye, the eye the implant was going to be put into perhaps, and have that person walk around and see how they function. Because basically what you're doing is, you're measuring their functional ability, not really trying to determine the exact dimensions of their field.

And so I think you could design a few steps could be done to determine what the success rate of that person for mobility purposes. If that's all we're looking for.

DR. MATHERS: Is that the kind of guidance you would like to have? Or could you tell us a little more?

DR. EYDELMAN: We'll accept this kind of guidance.

OPEN PUBLIC HEARING SESSION

DR. MATHERS: Okay. We had scheduled a break, but I think we are not going to take that unless the panel feels we must for five minutes.

Let's go on. We will now have a second open public hearing session, and if anyone in the room

did not hear the reading that I did originally on the conveying their - making this transparent, and their affiliation and association with the sponsors, then I'll be happy to read that again. I'm not sure that any new one is in the room such that I need to actually read that into the record again.

But I will remind everyone that this is intended to be a transparent process, and we would like to hear if you have affiliations and what they are.

So I will open this up for a second public hearing session. Is there anyone who would like to comment to the panel now, raise your hand and come forward to the microphone, or forever hold your peace.

All right. So I will close the open session. Now that the panel has responded to the FDA questions we will proceed - I'm sorry. Since there are no other requests to speak, we have closed that.

We will now proceed with the panel recommendations and a vote. I'm sorry, there's an FDA closure.

MS. THORNTON: We need to begin with the FDA for their final comments. You have up to five minutes.

DR. MATHERS: Sorry.

FDA - FINAL COMMENTS

DR. EYDELMAN: No comments at this time.

MS. THORNTON: No comments at this time.

DR. MATHERS: And for the FDA?

DR. EYDELMAN: I can only speak for the FDA.

DR. MATHERS: Will the sponsor approach?

SPONSOR - CLOSING COMMENTS

DR. GORDON: Judy Gordon on behalf of Vision Care. We would like to make some comments. Dr. Stulting and Dr. Heier are coming to the mike.

But in the meantime I just wanted to mention just a couple of things.

There were some questions here that came up that they will try to address. But I also wanted to mention that, Dr. Grimmett, the slides that you showed -

MS. THORNTON: Judy, can you get a little closer to the microphone, please?

DR. GORDON: Yes, of course.

The slides that you presented showing the anterior segments on UBMs, (ultrasound biomicroscopy) was a previous model of the IMT. And it may not have been clear in the publication, because I think at the time it was the only model. So I just wanted to

clarify that, because pictures do leave an impression.

And just another general comment. I think this was a little bit of a different panel proceeding for us as a sponsor, because we didn't have an opportunity to write responses to the specific panel questions, which I have found very productive in answering more of the minor things, although obviously there were significant issues that will require discussion.

But it left me regretting that we didn't have that opportunity. So if any of you have found it useful before, I hope that you might comment on that, because we certainly have been able to resolve many of the minor issues before coming to the panel and really focus on everything substantive, and that was a good example of one.

So I think Dr. Stulting is ready.

DR. MATHERS: So Dr. Stulting, are you prepared to address the panel?

DR. STULTING: Yes, sir.

Concern has been expressed that the outcome of this clinical study may have been a result of cataract surgery rather than the IMT. During protocol design sponsor proposed a study on patients with clear lenses, but FDA and others pointed out that

this would be virtually impossible to find subjects with significant AMD who did not have any lens opacities.

In fact the average age of the subjects in this study was 75 years. The lenses in these patients were clear enough to allow examination of the retina and fluorescein angiography preoperatively.

While the mean visual acuity in this group was 20/312 ETDRS, it is unlikely that this level of visual impairment was due to cataract.

Perhaps more telling in today's society is the fact that none of them had actually undergone cataract surgery by the time they were considered for the study.

None of the patients I treated had sufficiently advanced cataracts that I would have recommended cataract surgery alone.

My fellow investigators agree.

Finally 13 fellow eyes had cataract surgery in the opposite eye, and the average gain in vision was only one line in this group.

Randomization is attractive at first, but it would be difficult to balance populations on the basis of vision, age, sex, type of retinal disease, presence or absence of cataract, condition of fellow

eye, willingness to obtain follow up, et cetera.

It was mentioned today that 17 percent of patients had geographic atrophy, had a two or more line visual improvement when retested.

In this study 90 percent enjoyed an improvement of two or more lines of distance or near acuity. This is a significant change that is not a result of cataract extraction, vision training or improvement in macular degeneration. In fact 90 percent of the study population had severe or profound visual impairment at study entry, and this group had the greatest response to the IMT in terms of quality of life.

Questions have been raised about the outcome in eyes in which implantation was aborted or the device removed. There were 14 of these eyes. Mean LogMAR acuities from 12 of these eyes were within 0.02 units of their preoperative values; eight of these eyes were within one line of preoperative acuity; two lost two or more lines; and two gained two or more lines.

So there was not a poor outcome in this subset.

It has been suggested that visual outcomes be compared to the theoretical visual acuity that

accounts for the magnification produced by the device.

The IMT works because it magnifies. Increased acuity and increased functional vision for magnification is real for the patients who received the IMT as you heard this morning. They don't care whether they meet the theoretical improvement or not. They just know that they see better and that life is better.

I must admit that I was a true skeptic when I agreed to participate in the study. I thought they would have double vision. They might have difficulty ambulating, and that they would develop corneal edema.

I personally talked with each of the subjects at each visit because I'm the only anterior segment in our site. And I was surprised to find that these preconceived notions did not match reality.

There are advantages to the IMT other than cosmetic appearance or weight. These include an increase in the visual field; the ability to scan the environment without moving the head. It works without external support, freeing the patient to do other things that make them happy.

It's not easy to ride a bicycle or paint with a hand-held microscope - telescope. I'm

surprised that the overall improvement in the VFQ was questioned in some of today's comments. Indeed this is our best tool for measuring visual function. It tells us the IMT has a positive effect.

Steve, Jeff, and Allen and I were here today because we have experience with this device. We know that these patients would not be helped by cataract extraction alone.

We believe the IMT is a treatment modality that should be made available to selected patients who have few options. It is not a perfect device that cures macular degeneration or even stops its progress.

But the data support its approval under limited circumstances.

The sponsor appreciates the panel's concerns, and we thank them for their suggestions. I think we would all be best served by a limited approval so that it can be offered to older patients with high endothelial cell counts after informed consent.

This would permit collection of a long term data to address the questions posed today while making the technology available to those who are good candidates based on existing data.

Thank you.

DR. MATHERS: Thank you, Dr. Stulting.

That's your five minutes. One more minute? One minute.

DR. HEIER: Thank you. I appreciate the extra minute.

The purpose is just to address two other questions that were raised. First of all, the question about examination of the retina. We are able to see through the telescope, but just as importantly, we are able to see through the periphery as well. And we would hope that if a retinal detachment developed, we would be able to treat this by peripheral viewing.

We can also do a B scan, and we would be prepared if possible to treat these endoscopically.

With regards to the patients of macular degeneration and the types of lesions they have, we certainly would not advocate treating patients or implanting patients where the patients are being treated with ranibizumab at this time. Those are very different patients than the patients who were treated in this trial.

The patients in these trials, their exudated lesions were discoform scars, and had a great deal of fibrotic disease that would be unlikely to receive treatment if they developed recurrent disease.

Thank you for your time.

DR. MATHERS: Thank you. Thanks for being concise as well.

Okay. Now, that concludes that portion of the meeting. And now Ms. Thornton will read the panel recommendations options for premarket approval applications.

Ms. Thornton.

VOTING OPTIONS READ

MS. THORNTON: The medical device amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications, or PMAs, that are filed with the agency.

The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application, or by applicable publicly available information.

The definitions of safety, effectiveness and valid scientific evidence are as follows.

Safety: there is a reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence, that the probable

benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness: there is reasonable assurance that a device is effective when it can be determined, based on valid scientific evidence, that in a significant portion of the target population the use of the device for its intended uses and conditions of use when accompanied by adequate direction for use and warnings against unsafe use will provide clinically significant results.

Valid scientific evidence is evidence from well controlled investigations, partially controlled studies, studies and objective trials without matched controls, well documented case histories conducted by qualified experts, and reports of significant human experience with a market device from which it can fairly and reasonably be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of the device under its conditions of use.

Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinion are

not regarded as valid scientific evidence to show safety or effectiveness.

Your recommendation options for the vote are as follows. The first option is approval if there are no conditions attached.

The second option is approvable with conditions. The panel may recommend that the PMA be found approvable subject to specified conditions such as physician or patient education; labeling changes; or a further analysis of existing data. Prior to voting all of the conditions should be discussed by the panel.

Third option is not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe, or the data do not provide reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Thank you.

PANEL RECOMMENDATION TAKEN BY VOTE

DR. MATHERS: So we have three positions at this particular time. We can vote to approve. We can vote to not approve. Or we could approve with conditions in which case we discuss each of those

conditions, and then we vote on the issue of, is it then approvable by conditions.

I'd like to call for a motion to recommend approval, approval with conditions or not approvable, from someone in the panel.

Is someone prepared to make a motion on one of these three at this time, perhaps one of our main reviewers, or someone else?

DR. BRESSLER: I don't like the motion I'm going to make, because it's a major public health problem. But I would move that it not be approvable at this time, and we can do discussion afterwards.

DR. MATHERS: Is there a second for that motion?

DR. GRIMMETT: Second.

DR. MATHERS: So we will discuss this motion in our open panel session now.

If I could have Dr. Grimmett's comments on this - Dr. Bressler's, I'm sorry, Dr. Bressler's comments as someone who proposed the motion.

DR. BRESSLER: Well, I certainly appreciated Dr. Stulting's responses, and I consider them very strongly.

Nevertheless people do improve after cataract surgery in the setting of macular

degeneration. So I don't know if the outcomes with the surgery and the rehabilitation would be the same.

I know that we got the data very quickly on the missing people, but the ones that underwent implants, we need to know their data, look at it quietly, carefully, see if that brings us beyond the 10 percent safety margin of vision that was suggested as well as knowing are those visions out to one year, or where they were.

So I believe I don't have enough information at this time for the effectiveness.

And then for the safety, putting the whole package together, I'm concerned about the endothelial cell loss that was beyond what was thought to be safe and then the extrapolations do not bother me, but the data that we have bothers me that it was beyond what was thought to be safe.

So putting that whole package together, I'm reluctant to have it approved. I would vote not approved at this time.

DR. MATHERS: And Dr. Grimmett, would you like to comment?

DR. GRIMMETT: Michael Grimmett.

My comments, of course, made in my presentation explain the detail. But at this time the

chronic cell loss is what worries me the greatest. I certainly expect an acute surgical loss given how big the device is trying to put it in through a large incision. It's not the three-month break point that bothers me the most; it's the chronic cell loss.

I have every reason to believe, if I had to make a guess, that the cell loss will prove to be remodeling. It probably will take a lower rate in the future probably, just playing what I know about how surgical trauma acts on the cornea, but I don't think we have sufficient data to say that.

I think that if the excellent Specular Reading Center at Emory were to get the existing specular photographs and analyze the morphometric data, the percent hexagonality and coefficient of variation, they can easily determine do they or do they not return to their baseline levels, and what are the trends in those values to disprove an unstable endothelium.

Once that's disproved, and more data points are obtained at the two year figure, or perhaps 2-1/2 years, perhaps the morphometric data will allow them to better substantiate their choice of breakpoints. Perhaps they will find that the morphometric data, rather than the normal three-month

insult after standard cataract surgery, perhaps they will find that there is a nine-month insult after this procedure, and that the nine-month breakpoint is clinically substantiated by the morphometric data.

And then I believe that they will be able to seek future approval with the limitations that we've discussed. But at this time I do not have sufficient scientific evidence for an approval order.

DR. MATHERS: Now the rest of the panel I'm sure has thoughts on this.

This would be a good time to attempt persuasion of those who are yet undecided on this.

Yes.

DR. PALTA: Well, I'm trying to put together everything I've heard. Of course not being a clinician I guess I came up with a slightly different weighing of the risk-benefit here, considering how few treatment options there are, and the potential amelioration of risk by changing the labeling.

And I would like to hear more about that aspect.

DR. MATHERS: About amelioration of risk by modifying the entry criteria or by narrowing -

DR. PALTA: I'm thinking about the risk-benefit ratio here, and I thought that we would at

least - I thought that the benefit could potentially be pretty high, although I understand the province of perhaps not having considered all alternative explanations. Although I think that some of the comments of the sponsor seem to imply that those are unlikely to explain the benefits we are seeing.

So what I'm saying is that I thought that the discussions of how to reduce the risk perhaps changed the ratio enough to make this a difficult vote for me.

DR. MATHERS: Yes, Dr. Ferris.

DR. FERRIS: So as Neil said, I feel very conflicted here. I suspect, as Dr. Stulting said, that this device does help lots of patients. The problem I have, and where I disagree with Dr. Stulting, is imagine if we had 100 randomized controls that indeed were like the fellow eyes, and on average, even after the rehabilitation sessions and so on, didn't gain more than one line.

So there is a clear distinction between groups. And if I had to guess I would guess that that's true. If I have to explain to a patient here are your risks and here are your benefits, I don't know what to say on the benefits side. I think I know what to say on the risks side. And some of the risks

are unknown, and that happens all the time. That would be okay. But I don't know the magnitude of the benefit. And without the control group I'm not sure I ever can.

Now as I understood what Sally read, one of the choices that we don't have which would seemingly be an attractive choice to me, would be to let the company start marketing these in some limited way as we were discussing, and in the meantime do a concurrent randomized trial so that eventually they could have an appropriate way of telling people what the benefits are, but that's not one of our choices as I understand it.

So I'm left with what I consider a very difficult position.

DR. MATHERS: That's not a choice, but if we vote not to approve it at this time, it doesn't mean the device is not approvable of course.

DR. FERRIS: Oh, of course.

DR. MATHERS: With further data and information, that the FDA could work with the sponsor to obtain; is that correct?

MS. THORNTON: Yes, in the case of a not approvable vote, recommendation, from the panel, then we would ask you what you would like - what you feel

is necessary to bring this application into approvable state. So it's not dead in the water. We're asking you then for your thoughts on what would make it an approvable application.

DR. FERRIS: Yes, I fully understand that. And it's obvious what the issue is here. You either have an income flow or you don't have an income flow, and if you have to do another clinical trial that's very expensive, that's a problem. And if it got to the point that because this clinical trial was so expensive for a device that may have marginal economic value, and it doesn't get done at all, I think that would be a tragedy.

MS. THORNTON: We do have to consider existing data. That's the bottom line.

DR. MATHERS: Yes, Jayne.

DR. WEISS: So with the thought of needing to consider the existing data, and the realities that we all have a sentimental reason for wanting to have patients be able to have access to this, and yet clearly this goes with the data we have in hand at this session, we do not have valid scientific data that shows reasonable safety and efficacy.

We have anecdotal data saying that these patients didn't have bad cataracts, but that doesn't

qualify as valid scientific data.

What I would ask both Neil and Michael is, in terms of the aspect of reasonable efficacy, I think in terms of reasonable safety the endothelial cell data seemed to speak against it, but for reasonable efficacy would there be any questions that you could ask from the present study for the sponsor to go back and glean more data that might convince you of reasonable efficacy short of doing another study with a control group which of course would be very costly and much more difficult?

I don't know if the sponsor could get us information as far as level of cataracts in each of these patients to confirm Doyle's observational comment. But is there anything here for either one of you who were reviewers, or Dr. Brilliant as well, that could rescue this from an efficacy standpoint.

DR. MATHERS: Dr. Bressler.

DR. BRESSLER: So certainly we can get as much information as they have in the time out for the 11 cases that were halted and considered not successfully implanted, and we can get the information on the eight cases that were removed, and we can get the last information they have on people that didn't come - the 13 people that didn't come in for the end,

that probably includes some of the eight that were not -- where the implant was removed, and look at that data scientifically and make a judgment if we're very comfortable that that did not increase the loss of vision that has been reported for the group we have. So that helps.

Because one of the unknowns is, would that have increased the loss of data, because that keeps us from knowing the efficacy?

I am still concerned, I can't think of other things right now that would take care of the NEI-VFQ and the visual acuity information without the controls, because this is what happens when you take a cataract out, some of these people do improve, and some of them do have better NEI-VFQ, either because of the cataract coming out or getting better at their eccentric vision, et cetera.

So this is a very hard answer to make without controls.

DR. MATHERS: Dr. Grimmett, did you have a comment in response to Dr. Weiss' question?

DR. GRIMMETT: No, my primary concern is with safety, and if the sponsor produces sufficient data, which they should be able to easily do, then I believe that it could be approvable with conditions.

I don't really have an effectiveness gripe at this point.

DR. MATHERS: Yes, Dr. Niksch.

MS. NIKSCH: I have a question, and then a couple of comments.

Just for clarification there's a motion that's been made, and then a vote will be taken, and if that vote doesn't carry the majority, then is another motion able to be made? Just to clarify the numbers?

DR. MATHERS: Yes.

MS. NIKSCH: Okay, a couple of comments. One, as many of you have commented, it's unfortunate that there seems to be a lot of open questions that came from the reviewers, and unfortunately the sponsor has not had a chance to really - I don't know if that's a matter of policy or timing, that your comments weren't distributed so that that could have been included in their presentation.

But as you can see, that would have perhaps been very beneficial to the remaining panel members to ease any additional doubts and make sure everyone has all the information in order to make the most informed decision.

With that being said, just again, because

the vote has still not been voted on, I urge you to consider the dataset that exists today; what additional questions you may have on that dataset, the sponsor could go back and address to, again, try to get this to an approvable with conditions so that this device can be used in a specific population, or else it probably will not be used for five or more years if a new study from the ground up has to be done.

DR. MATHERS: Dr. Heuer.

DR. HEUER: I need some help in understanding what existing data is. Is it only what's in these 11 volumes, or does it include going back and looking at the existing endothelial photographs and getting morphometric data to add to Dr. Grimmett's concerns.

DR. MATHERS: I believe that existing data is that which you have seen. However, of course, if extra data could be extracted, then you wouldn't have to do another study. You could come back -

DR. HEUER: I guess my question, to be more specific, is could we vote to make it approvable pending morphometric proof that -

DR. MATHERS: No, we're supposed to go on available data. Existing data. I believe so.

DR. WEISS: I would just question, and

perhaps Malvina can answer this, or the agency can answer this, if the sponsor has the specular microscopic photographs, which we of course don't have access to, and they could go back and look at that existing information that they could extract data, is that acceptable to consider?

MS. THORNTON: Not at this time.

DR. WEISS: Could that be a condition?

DR. MATHERS: That's not a condition.

MS. THORNTON: There are no conditions with not approvable.

DR. MATHERS: Yes.

DR. EYDELMAN: If it is not approvable, the sponsor still has an option to come in with an amendment after the not approvable, with additional data for consideration.

DR. WEISS: What I'm asking, Malvina, is if there is a vote for not approvable that does not pass, and one of the conditions for passage is getting additional data from the specular microscopic photographs that the panel wasn't privy to, is that considered existent data.

That's only if the vote for not approvable didn't pass. If a vote for not approvable passed, then it would be a nonissue.

DR. EYDELMAN: Well, it's difficult to make a recommendation pending data that wasn't collected. So whether the sponsor has it or not, we have never been privy to it. So I think the panel would be - it would be helpful if you made recommendation pending data that we know exists.

MS. THORNTON: Also I'd like to clarify something that was mentioned by Ms. Niksch. The sponsor did not have the primary reviewers' reviews. The panel did not have the primary reviewers' reviews until today.

DR. HAIK: I was just wondering, is it true that the process would die for five years? Or are there many other avenues for them to come back? It was implied, wasn't it, that if this didn't go through today that this technology would disappear?

MS. NIKSCH: Barbara Niksch. I was just making a statement that if a sponsor has to go back and design a brand new study, particularly if a concurrently controlled randomized study, and looking at how long it took them to enroll their 200-plus subjects at 28 sites, it's a five-year process to bring it back to panel.

DR. EYDELMAN: One more comment. While the panel can't make a recommendation of approvable

pending data that we don't know whether it exists, you can certainly, if you do choose to vote not approvable, each one of you can recommend the data that you would like to see in order to change your recommendation. And then if the sponsor does possess that data, they don't need to wait five minutes - five years. (Laughter.) They can submit it in five minutes.

MS. THORNTON: Four minutes.

DR. MATHERS: Yes, Dr. Huang.

DR. HUANG: First, I think we have become victims of our instruments. I really think this study was probably previously communicated with the FDA, with the conditional communication with FDA to go forward. And then now we are looking at the data, and from - first I want to clarify before I make the following statement. I'm not impressed with the safety data, but I'm not impressed with the efficacy data.

With that being said, I do feel that the study is well conducted. However, that there is a lot of room for improvement. But that doesn't qualify this study to be disapproved.

As has been said, there are two issues: one is the efficacy issue. I think that's the easiest

one for me to sort out. We have shown that using the telescope externally is equivalent to using the internal device, so in that regard this device in my mind is at least efficacious, and may have some theoretical advantage from the patient's perspective, and maybe even from the physician's perspective.

Second, the safety issues, that you know, to me, that is surgery, is not much worse than all previous cataract surgery. Twenty years ago, cataract surgery, we don't know much about intraocular implant, and then we have all kinds of designs which may or may not be physiological.

If you look at Dr. Born's two studies in the zero density, in 1994 and 2003, the difference in terms of the endothelial density decrease rate is dramatically different between the two sets of cataract surgery.

Those are both intracapsular cataract surgery, just like these are current surgery. So 20 years ago there were 20 percent of the endothelial loss. And most of those patients, I mean granted some of them didn't require future corneal transplantation surgery, but most of them did enjoy their success of their initial cataract surgery, whether we like it or not today.

But then the second set of the surgery is that 10 years later that endothelial loss is 10 percent. And I'm not convinced that 10 percent of the patients is not eventually going to have a problem.

So based on that two safety issues and the efficacy issues, I think this device is worth looking into it. But we can provide the other conditional studies such as the morphometric data, or such as other safety issues.

But I don't think this should be nixed at this moment.

DR. MATHERS: Okay. I want to call for a vote on this. I think we could talk for a long time.

This is a vote that on the motion that this device in its current form with our current data set is not approvable at the present time.

And I'm going to go around the room and ask for your vote on this.

Dr. Ferris.

DR. FERRIS: I vote that it is not approvable.

DR. MATHERS: Dr. Szlyk.

DR. SZLYK: I don't agree that it's not approvable.

DR. MATHERS: What is your vote?

DR. SZLYK: No.

DR. MATHERS: Dr. Haik.

DR. HAIK: I vote it's not approvable.

DR. MATHERS: Dr. Brilliant.

DR. BRILLIANT: I vote that it's not approvable.

DR. MATHERS: Dr. Sunness.

DR. SUNNESS: I vote that it's not approvable.

DR. BRESSLER: I vote that it's not approvable.

DR. BURNS: I vote it not approvable.

DR. MATHERS: Dr. Huang.

DR. HUANG: I don't agree with current vote.

DR. MATHERS: So you vote no on the motion?

DR. HUANG: Yeah, vote no.

DR. MATHERS: Dr. Edrington.

DR. EDRINGTON: Not approvable.

DR. HEUER: Regrettably yes to the motion.

DR. BRESSLER: Yes.

DR. MATHERS: Dr. Grimmett.

DR. GRIMMETT: Yes, to the motion, not approvable at this time.

DR. MATHERS: Dr. Palta.

DR. PALTA: I vote no.

MS. THORNTON: No meaning?

DR. PALTA: No to the motion.

DR. MATHERS: No to the motion.

What is the tally on that vote?

MS. THORNTON: Eleven votes for the motion of not approvable; three votes against the motion of not approvable.

DR. MATHERS: And no abstentions?

MS. THORNTON: There are no abstentions.

DR. EYDELMAN: Are you sure you have the numbers right?

DR. EDRINGTON: I have voting for the motion of not approvable: Dr. Ferris, Dr. Haik, Dr. Brilliant, Dr. Sunness, Dr. Bressler, Dr. Edrington, Dr. Burns, Dr. Heuer, Dr. Weiss, Dr. Grimmett.

Voting against the motion of not approvable: Dr. Szlyk, Dr. Huang, Dr. Palta.

DR. MATHERS: Clearly the motion carried. That is, we voted to not approve at the present time.

Now we need to go around the room and for the record -

DR. EYDELMAN: I got 10, Sara.

MS. THORNTON: Yes, I'm sorry. I just - I forgot the other part. There are 10 for the motion of

not approvable; three against the motion of not approvable.

FINAL PANEL COMMENTS

DR. MATHERS: We're going to go around the table, and we're going to ask every person to comment on their votes, the reasons why they voted to have in the record.

MS. THORNTON: For the record Dr. Ferris left out of here, and is not going to be available to stay -

DR. EYDELMAN: He had a flight to catch.

MS. THORNTON: Yes, he had a flight. And he did not have an opportunity to put his comments about his vote for the motion of nonapproval into the record.

DR. MATHERS: I'm going to start at the other side of the room. Dr. Palta?

DR. PALTA: Yeah, I thought that with some conditions that we had discussed the benefits would just slightly exceed the risks.

DR. MATHERS: Thank you. Dr. Grimmett.

DR. GRIMMETT: This is Dr. Grimmett. And echoing what I've said before, I voted not approvable because the current data does not substantiate the safety of this device from an endothelial standpoint.

However, I do believe that interpreting the existing photographs will supply morphometric data which will lend credence to the theory of prolonged remodeling, and that the sponsors should be able to show an appropriate cell loss rate which will reduce my concern about safety.

DR. MATHERS: Dr. Weiss.

DR. WEISS: I regrettably had to vote not approvable because of the guidance that we were given by Sally Thornton. The scientific evidence that was presented did not show reasonable safety because of the endothelial cell loss rate, and the chance that patients might need corneal transplant as years go by.

And they also did not show reasonable efficacy because of the lack of data presented here to the panel of the confounding variables that could have also improved vision such as removal of visually significant cataracts.

I hope the panel will be able to see the data or FDA will be able to see the complete data set so that this can get approved with reasonable assurance to the public of safety and efficacy in the future.

DR. MATHERS: Dr. Heuer.

DR. HEUER: I was reasonably convinced

about the efficacy, at least as far as I can be without the gold standard; but the safety issue remains a major problem, and I think we not only need the morphometric analysis, but we need a better understanding of why these people are continuing to lose endothelial cells at a faster rate if that trend continues, and so we need a longer track record rather than extrapolating.

I think to get that we're probably going to have to have ultrasound biomicroscope exams on everybody to get some idea if the people losing cells are the ones with it closer to the cornea, otherwise it remains a really knotty issue.

DR. MATHERS: Dr. Edrington.

DR. EDRINGTON: My concern also was the existing data set on the endothelial cell counts; that's my major concern. I'd love to see that turned around so patients could benefit by this.

DR. MATHERS: Dr. Ferris is not here.

Dr. Szlyk.

DR. SZLYK: I did think that we have - I did not agree with the motion. I did think that we had sufficient data for those in the older age ranges, and that we could potentially approve with certain conditions that would affect the inclusion criteria.

DR. MATHERS: Dr. Haik.

DR. HAIK: Like many of the others I was conflicted over this, and I very much want to see this available to patients. On the other hand, and I very much respect the people that presented the data to us, the principals involved.

But in all honesty based on the evidence that was presented to us, based on the FDA interpretation, based on the review of the superb experts in this group, as much as my heart wants to vote one way, I have to vote against approval.

DR. MATHERS: Dr. Brilliant.

DR. BRILLIANT: I think from a low vision point of view, I think it is a potentially good type of device, and I think it would have a future.

But from the data that's available at this point, the safety and efficacy, I feel a little uncomfortable about saying that it is sufficient.

DR. MATHERS: Dr. Sunness.

DR. SUNNESS: I also regret that I have to vote not approvable. But I do think that there are things that the sponsor can do to have it come back and possibly be approvable with conditions.

I too was primarily concerned with the safety issues. But in terms of the efficacy issues,

as I said before, I would like to see data on what happened with the fellow eye, on specifically is the patient actually using this eye to do tasks, such as reading; some assessment of their peripheral function; direct inquiry and other things.

And I assume that our recommendation could also be to go back to current patients and get some of that data, which should be available.

DR. MATHERS: Dr. Bressler.

DR. BRESSLER: So I agree with all the comments, emotionally. These patients need something that does indeed work like this. But as Sally read to us, it has to stand on its own merits by the data that's here, and we have to make a decision, scientifically, to advise the FDA.

And in terms of the safety, that's been said over and over again, so I won't repeat it except that I believe it has not been shown yet from the information we have to be safe.

But I also believe in terms of the efficacy, this is a very difficult task to sort out in terms of what is the cataract, what is the learning to use eccentric fixation over a year's time, what is the drive by the patient to try and improve.

We have multiple trials showing NEI-VFQ

improving in shams over time in this condition, so you really unfortunately need a control.

I agree, I wish this was known at the start, and that the funds could have been gotten to design it that way.

It wasn't, so we have to deal with what we have, and I believe scientifically the efficacy isn't there yet in this very complex situation.

It could have been. This design is okay, had there been an overwhelming vision response. I don't think it was overwhelming enough to say that we're not reasonably assured that it wasn't just all the other factors that we said.

So unfortunately we have to do that, and unfortunately, I made the motion.

DR. MATHERS: Dr. Burns.

DR. BURNS: My primary concern was safety, concerning the longer baseline understanding what's happening to the endothelial cell count.

But also it would be nice to be reassured that a good retinal exam could be provided for future treatment of these patients, and this could be obtained by just providing us with scientific evidence to that effect.

Efficacy was not such a concern for me. I

think the patients are quite pleased with it for whatever reason, that does sway me quite a bit. I'd like better data, but primarily safety was my concern.

DR. MATHERS: Dr. Huang.

DR. HUANG: I voted against the motion based on my belief that I don't think extrapolation of the existing data can be compared with the lifetable analysis.

DR. MATHERS: I think I'll give my comments at this time, and then move to our patient and industry representative.

I did not vote. However, I thought that the safety issue was not resolved; that it still is a major concern.

However, I am not of a mind to say that the extrapolation that we can do at two years is definitive by any means. And I am thinking about data from corneal transplant patients, which shows a very high loss rate for 10 years, but then falls off.

Anything that would ameliorate this distant end would be of great benefit, and I suspect that that's going to be the case here. However, we do not have that data, and at this point - although I think that we can get it without doing another study.

I was moved by the potential efficacy of

this, although I think it's not necessarily dramatic, it certainly would be in many cases helpful to these people, but I think the confounding issue of the cataract and other variables that are involved here were less sure than the efficacy.

But I was not strongly opposed to it - to calling it efficacious. And I hope that the sponsor will be able to come back and make this an acceptable device. We certainly would like that, and would benefit. But we have to go - absolutely have to go on the science, and the science did not actually work here.

Now I'd like to hear from our industry representative.

COMMENTS FROM CONSUMER AND INDUSTRY REPRESENTATIVE

MS. NIKSCH: Barbara Niksch, thank you.

First of all, as you know the study was conducted under an approved IDE, which for those of you who don't know, undergo several rounds of negotiation with the agency, as Dr. Huang pointed out.

Unfortunately sometimes during the study you do learn things, and you understand there might be additional data that needs to be gathered, as in the case of today that you've identified several issues.

Notwithstanding, I think that this is a

novel, first-of-a-kind device that many of you do agree does have clinical utility, and it was a challenging population and a challenging study that the sponsor undertook, and for that they should be commended for this innovative activity.

My hope is continued collaboration with FDA, the sponsor and this panel to work together and collaborate, to come up with the least burdensome approach to get this device in the hands of physicians in this country to treat the American population.

Thank you.

DR. MATHERS: Mr. Bunner.

MR. BUNNER: First of all, I guess I'll find my way in my role with this committee, and I know that part of my role is liaison to advocacy and consumer groups for information coming into the panel, and response, and also following the process today, information to go back out to those groups, that they would like to get that kind of information from me.

And based on that, I have to say that I'm very appreciative of the role of the FDA, this very distinguished panel, and really the role of the sponsor, coming in today knowing not that much on the topic, although I did wade through all the materials handed out. I really do feel as a consumer I feel

very well informed on the topic. So I appreciate all of your support with that today.

One of the organizations I represent is Prevent Blindness in America, and one of our missions is the prevention of blindness, which of course this instrument does not address. I think Dr. Stulting had mentioned that. Nor does it address the preservation side.

So I'm hearing a lot of deliberation, I was initially overwhelmed by the fact that on the preservation side issue there was data showing that perhaps this responded to the contrary, and was to some extent sight threatening with all the discussion on endothelial cell loss.

At the end of the debate today, though, I thought about from a consumer standpoint the whole issue of risks we have in society, and a lot of the risks we have in society are a choice to wear or not wear seat belts; to wear or not wear helmets on motorcycles. We are presented as adults with lots and lots of risks.

Obviously there is a device that is presented here today that showed at least to folks who gave testimony and to sponsors a device that seemed to give hope for some people.

And it did seem from a consumer standpoint that with informed risk this would still be a choice that consumers could make.

So I respect the decision that was made by this panel, and I have to admit I flip flopped back and forth all day long on the issue.

At the end of the day I would have loved to have seen this be an option that was made available to consumers with conditions.

So I'm certainly very hopeful that the sponsors - I'm sure this is a monumental challenge to them - will be able to come back to meet the data requirements presented by this distinguished panel.

And I appreciate my opportunity to participate with you all today.

DR. MATHERS: I would like the panel now to address how the advising the sponsor and the FDA how we might bring this to a more positive conclusion. Because I think that it certainly ought to be evident that the hope is that this can become something that is useful.

We definitely feel that something in this line has great potential; probably we're not far off the mark here, and if we could give some guidance it would be - as we already have, but if someone wants to

make additional comments, for instance regarding limiting this to a particular subset of the AMD limited age range, going back and getting follow up data for another period of time when the existing group, looking at anterior segment structure, has Dr. Grimmett has suggested, these have all been suggested.

Would someone like to give additional comments at this time? Dr. Burns.

DR. BURNS: I'd just like to ask for a point of clarification. Because I wouldn't want to suggest limiting from the sponsor's point of view if it meant they had to do a design all over again.

So if we suggested they limit it to a certain age range, that wouldn't require any trial.

DR. MATHERS: No, but if they - and - right, the FDA and the sponsor would work out a circumstance such that a reapplication might have different parameters, based on data that they can then reorganize or collect without necessarily doing - obviously you could do an entire study, five years, a lot of money. And sure, you could do - now that you know what you want you could do it. But short of doing that, collecting additional information on this group that would give instruction so that if you made a narrower group the focus of the application that it

would then be approvable for that group.

Get it on the market, and then see how it goes. Is that - am I interpreting this correctly? Okay.

Dr. Haik.

DR. HAIK: I had a couple. I know most of the people involved with this study, and they are extraordinary people. I'm a little confused if you're the Specular Microscopy Reading Center, at one of the great institutions in the United States, why you wouldn't have done the morphometric data, why you wouldn't have taken multiple specular micrographs knowing that - even I know that there are - corneal endothelium tends to be denser than the central part. Pachymetry is nothing to it in terms of adding that to a study. Some of those things kind of confused me, as well as just missing just basic gonioscopy.

I mean maybe you did have UBM, or maybe UBM was too late, or there was too much refraction off of things.

But there are some key things that I would have been prepared for coming into this. And one would be for a retina, and one would be with the increasing - I mean I would either know whether I could visualize it or not. I'd explain really well

how I'd visualize it or not. Somewhere in there, I mean maybe you can see around the haptics, and see through the capsule, or see through an iridectomy site or transilluminate. But I don't really know that, and without knowing that, knowing I'm limited to a posterior pole view, and knowing the number of diabetics and number of people with peripheral retinal disease in the United States, I'm just a little bothered that those things weren't just wiped off the map so we didn't have to worry about them.

Because I know they were thought about by the people involved.

And the other one that bothered me was the uveitis, was the inflammation. And then the comment that had to do with the vitritis for six months because KPs - or precipitants coming on the lens from the iris - that kind of explanation to me was subpar for the quality of people that are addressing the issues that we're talking about.

So I'll be honest with you, I probably would have voted very strongly for doing this based on the patients that are there, based on all the others, but I was not convinced that going along with this was doing no harm, and I think I could have been.

DR. MATHERS: Okay, thank you.

Dr. Sunness.

DR. SUNNESS: When the sponsor responded, I agreed with what he said in terms of choice of patients. So I just wanted to backtrack, to say what I said before stands, that is, I think bilateral geographic atrophy patients with choroidal neovascularization are a good group. I think that people who have geographic atrophy in one eye and CMV in the fellow eye are not a good group, because it's like to get new choroidal neovascularization in the involved eye.

But I do agree with you that if a patient had large discoform scars, and was unlikely to be eligible for any sort of treatment they would be reasonable to have this as well.

DR. MATHERS: Dr. Bressler?

DR. BRESSLER: I have to sit down and figure out the best way to approach this.

And again, beside the safety, as you heard, I was uncomfortable with the efficacy because of the reports that are in the literature or are coming out about sham and changes in the NEI-VFQ, so we have to take that into account in this AMD population.

And visual acuity changes following

cataract surgery with scars. And this information will be coming out in the literature over the next year, and we can direct it all to the FDA and the sponsors, and make sure we're paying attention to it.

That's what weakens the efficacy data for me. Those have only been presented at meetings. This is information on cataract surgery in the submacular surgery trials in people that had scarring there, what happened. Now their cataracts were probably denser; that's the problem. And this is NEI-VFQ information coming out of the Ranibizumab trials that were assigned to sham.

But again there will be information coming out. That being the case, if you do have a large difference in what you're helping these people with, if this 73 percent two or more line improvement at one year is much bigger than a 25 percent in two or more lines in an equivalent group, then you don't need a large trial to show that.

Now if it's 73 percent versus 50 percent then you're starting to get there, but if it is 73 versus 50 percent, then the variability that we're talking about is leaving me from being certain with this data that we have a difference.

So I would look into the power of what you

have of doing a smaller trial where you do control that because of this other data that's coming out to make us wonder, although I take fully into account what Doyle said about, he doesn't believe these cases had bad cataract, but it's just hard to know without that information.

So I'm straining how not have to do yet an additional trial, but maybe an additional small trial with the additional safety information from this larger trial would do it if it has a big enough difference.

DR. MATHERS: I don't think particularly well on my feet in public being recorded. I prefer to think about it and reflect on this. For much of the panel, as the sponsor also experienced, got a lot of information over a short period of time. Much of it was new. Much of it was very worthwhile to consider.

I'm going to suggest something a little bit out of the ordinary that the FDA and the sponsors have an extraordinary opportunity to utilize some of the best expertise they'll ever get about this project, because we really do want this to go. We want it to work.

And if the panel members feel like commenting after the meeting, I hope that that would

not be trashed, because maybe we could all work together in this process to improve this, and I don't see why panel members couldn't make suggestions later if they think of something in the middle of the night.

DR. EYDELMAN: Rather than extraordinary, this is actually how we do business, and that's why we value all of your input, and then we read through the transcript, ad nauseam, until we make sure that we understand what each one of you meant.

DR. MATHERS: If there are no other comments, then I think I will adjourn the meeting.

Closing remarks?

FINAL PANEL REMARKS

DR. MATHERS: Well, I have given my statements, and how I felt about the product, or the PMA, and the motion, and my sense of guidance to the sponsor.

I would like to ask Dr. Eydelman if she has some further comments, closing remarks to give to this committee.

DR. EYDELMAN: I just wanted to thank all of the panel members for their deliberations and for their thoughts and preparation that it took to conduct today's complicated proceedings, and I just want to make sure that the sponsor doesn't get discouraged.

We too understand that it is a very difficult trial to conduct, and we are open to working with you interactively and trying to see what may be done next.

DR. MATHERS: Okay, the chair would also like to personally thank Sally Thornton for assisting in my inaugural meeting.

And with that I will close this committee.

(Whereupon at 5:28 p.m. the proceeding in the above-entitled matter was adjourned)