SUMMARY MINUTES

OF THE

109th MEETING OF THE

OPHTHALMIC DEVICES PANEL

OPEN SESSION

July 14, 2006
Hilton Washington D.C. North
Gaithersburg, Maryland

Ophthalmic Devices Panel Meeting

July 14, 2006

Attendees

Chair
William D. Mathers, M.D.
Casey Eye Institute
Oregon Health Sciences University
Portland, OR

Executive Secretary
Sara M. Thornton
Food and Drug Administration
Rockville, MD

Voting Members
Neil M. Bressler, M.D.
Wilmer Eye Institute
The Johns Hopkins University School of Medicine
Baltimore, MD

Stephen A. Burns, Ph.D.
Indiana University School of Optometry
Bloomington, IN

Timothy B. Edrington, O.D.
Southern California College of Optometry
Fullerton, CA

Dale K. Heuer, M.D.
Medical College of Wisconsin
Madison, WI

Andrew J. Huang, M.D., M.P.H.
University of Minnesota
Minneapolis, MN

Consultants
Richard Brilliant, O.D.
The Eye Institute
Pennsylvania College of Optometry
Philadelphia, PA

Frederick Ferris, M.D.
National Eye Institute
Rockville, MD

Michael R. Grimmett, M.D.
Grimmett Eyecare, LLC
Palm Beach Gardens, FL

Barrett G. Haik, M.D.
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Madison, WI

Janet S. Sunness, M.D.
Hoover Services for Low Vision and Blindness
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Janet Szlyk, Ph.D.
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College of Medicine
Chicago, IL

Jayne S. Weiss, M.D.
Kresge Eye Institute
Wayne State University
Detroit, MI

Industry Representative
Barbara A. Niksch
Visiogen, Inc.
Irvine, CA

Consumer Representative
Richard T. Bunner
Private Public Health Consultant
Zanesville, OH

FDA Participants
Malvina B. Eydelman, M.D.
Director
Division of Ophthalmic Devices

Aron Yustein, M.D.
Deputy Clinical Director
Office of Device Evaluation

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

Sousan S. Altaie, Ph.D.
Scientific Policy Advisor
Office of In Vitro Diagnostic Device Evaluation and Safety

Danica Marinac-Dabic, M.D., Ph.D.
Chief, Epidemiology Branch
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Don Calogero, M.S.
Biomedical Engineer
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Bruce Drum, Ph.D.
Vision Scientist
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CALL TO ORDER AND INTRODUCTIONS

Panel Chair William D. Mathers, M.D., called the meeting to order at 8:48 a.m. He asked the panel members to introduce themselves. **Panel Executive Secretary Ms. Sara M. Thornton** introduced Ms. Karen Warburton, who will be assuming the role of Executive Secretary following Ms. Thornton's retirement next May. Ms. Thornton announced that the panel meeting scheduled for September 19-20, 2006 had been canceled.

Ms. Thornton read the appointment to temporary voting status for Richard Brilliant, O.D.; Frederick L. Ferris, M.D.; Michael R. Grimmett, M.D.; Barrett G. Haik, M.D.; Mari Palta, Ph.D.; Janet S. Sunness, M.D.; Janet Szlyk, Ph.D.; and Jayne S. Weiss, M.D. She then read the conflict of interest statement. Waivers were granted to Neil M. Bressler, M.D., and Dale K. Heuer, M.D.

FDA AWARD PRESENTATION

Aron Yustein, M.D., Deputy Clinical Director, Office of Device Evaluation, presented an award to Jayne S. Weiss, M.D. in recognition of her past service as Chair of the Ophthalmic Devices Advisory Panel.

DIVISION UPDATES

Malvina B. Eydelman, M.D., Director, Division of Ophthalmic Devices, related the loss of several people at the Division, including Dr. Ralph Rosenthal, the former Division Director from 1996 to March of 2005, who passed away in January of 2006, and Mr. David Whipple, who retired in May of 2006. Dr. Eydelman then introduced Dr. Kesia Alexander as the new Chief of the Intraocular and Corneal Implants Branch, and new Division scientists Dr. Tina King, Ms. Claudine Krawczyk, Dr. Joseph Hutter, and Dr. Mark Robboy .

BRANCH UPDATES

Kesia Y. Alexander, Ph.D., Chief, Intraocular and Corneal Implants Branch, began by reviewing premarket approval applications (PMAs) and humanitarian device exemptions (HDEs) approved since the last panel meeting. The PMAs approved are P030023, approved April 27, 2004 for Ophtec's Oculaid Stableyes Capsular Tension Rings; P030028, approved September 9, 2004 for Ophtec's Artisan Verisyse Phakic Intraocular Lens (IOL); P040020, approved March 21, 2005 for Alcon's Acrysof IOL; P840064, approved March 23, 2005 for Alcon's Discovisc Ophthalmic viscosurgical device; P930014, approved September 14, 2005 for Alcon's AcrySof Single Piece IOL with Toric Optic; P010059 for Morcher Cionni Capsular Tension Rings; and P030016, approved December 22, 2005 for STAAR's Visian Implantable Collamer Lens. One HDE, H04002, was approved on July 26, 2004 for Additions Technology INTACS prescription inserts for keratoconus.

Dr. Alexander stated that recent cases of Toxic Anterior Segment Syndrome (TASS) are under investigation. She said that one branch member, Ms. Susan Gouge, had passed away following a car accident in November of 2005.

Everette T. Beers, Ph.D., Chief, Diagnostic and Surgical Devices Branch, said his branch had not had any staff changes since the last meeting. He then reviewed the eight PMAs approved since that time: Monovision's Refractec ViewPoint CK System, approved March 16, 2004; the VISX Wavefront-guided hyperopia plus astigmatism in December 2004; VISX Wavefront-guided mixed astigmatism in March 2005; VISX Wavefront-guided high myopia plus astigmatism in August 2005; Alcon's custom cornea system for wavefront-guided myopic astigmatism in June 2004; Alcon's Wavefront-guided LASIK for correction of hyperopic astigmatism and Wavefront-guided LASIK for correction of mixed astigmatism, both in May 2006; and WaveLight Allegretto received approval in April 2006 for conventional LASIK for mixed astigmatism.

James F. Saviola, O.D., Chief, Vitreoretinal and Extraocular Devices Branch, began by noting the retirement of several individuals from the branch, including Dr. Daniel W.C. Brown, a former executive secretary for the panel, Dr. Jimmy Chen, Ms. Eleanor McGhee, and Dr. Linda Cohen. Three PMAs approved since the last meeting are P040045 for the Vistakon Oasis senofilcon silicone hydrogel lens in December 2005, P010062 for the Euclid Orthokeratology contact lens for overnight wear (marketed by Bausch & Lomb as the Boston Vision Treatment System) in June 2004, and P040029 for Dr. John Szabocsik's JSZ Orthokeratology contact lens (the same device as the Euclid lens) in September 2004.

Dr. Saviola noted that postmarket surveillance was underway to address concerns about the use of overnight orthokeratology lenses in patients under 18 years of age. Referring to the recent Fusarium outbreak associated with Bausch & Lomb's ReNu MoistureLoc, Dr. Saviola thanked the Mycotics Disease Branch at CDC, various state health departments, the individual doctors who reported the outbreak, and various professional organizations for their efforts in dealing with the outbreak. FDA is still trying to definitively determine the cause of the event. Dr. Saviola also reported that FDA is working with the American National Standards Institute (ANSI) on the issue of contact lens groupings related to the new silicone hydrogel lenses. Finally, he announced that the Food, Drug, and Cosmetic Act had been amended to establish that all contact lenses, including plano or decorative, noncorrective contact lenses, are classified as devices.

CRITICAL PATH INITIATIVE IN MEDICAL DEVICES

Sousan S. Altaie, Ph.D., Scientific Policy Advisor, Office of In Vitro Diagnostic Device Evaluation and Safety, gave a presentation on FDA's Critical Path Initiative, a serious effort to make product development more predictable and less costly. Critical path tools are used in the assessment of safety to predict whether the product will be harmful; in proof of efficacy to determine if it will have medical benefits; and in industrialization to ensure the product is manufactured with consistent quality.

Dr. Altaie described some of the differences between devices and drugs in the critical path track. For devices, biocompatibility databases are one example of a safety tool; surrogate endpoints and computer simulation modeling are possible effectiveness

tools; and practice guidelines and validated training tools are examples of industrialization tools.

CONDITION OF APPROVAL STUDIES

Danica Marinac-Dabic, M.D., Ph.D., Chief, Epidemiology Branch, Office of Surveillance and Biometrics, discussed recent changes in the condition of approval study program. FDA has authority to require manufacturers to conduct post-approval studies.

An internal evaluation of the program revealed that the Center for Devices and Radiological Health (CDRH) had limited procedures for tracking these studies, due to deficient information technology (IT) systems; a high turnover of lead reviewers which resulted in a lack of continuity and follow-up; and a lack of premarket resources.

The program was transferred to the Office of Surveillance and Biometrics to better utilize resources. An automated tracking system was also established for the program.

Epidemiologists review the PMA and are charged with development of a postmarket monitoring plan during the premarket review process, development of postmarket questions, and design of study protocols. Dr. Marinac-Dabic described a comprehensive approach including medical device report (MDR) analysis, literature reviews, and external databases. Furthermore, significant findings will be reported to the advisory panels.

The benefits of these changes are better designed post approval studies, tracking of those studies, and collection of more complete postmarket information. There will

also be an attempt to identify postmarket questions prior to panel meetings so that any questions raised can be better addressed.

Dr. Ferris asked whether postmarket surveillance was limited to observational studies. Dr. Marinac-Dabic replied that randomized clinical trials could be done but are generally avoided because of the ethical issues and the burden to sponsors.

OPEN PUBLIC HEARING

Mrs. Janet Grant talked about the impact of the implantable miniature telescope (IMT) on her life. It has enabled her to return to reading, her painting hobby, and bike riding.

Mr. **Edward Nungasser** discussed how is life has been changed by the IMT and asked the panel to give the PMA serious consideration.

R. Doyle Stulting, M.D., Ph.D., Emory University, read a letter from one of the clinical investigators, Susan Primo, O.D., who was unable to attend the meeting. She said the IMT was the first surgical option to help her visually impaired patients. While she was initially concerned about her patients' ability to get around, the rehabilitation sessions made this much less of an issue.

Another concern was different image sizes, known as aniseikonia, but after several months most patients did not have any issues with this. Dr. Primo suggested that cortical plasticity might explain the brain's ability to compensate.

Internal placement of the IMT allows for significant increase in visual field and elimination of the ring scotoma associated with external telescopes, and placement near the center of the eye's rotation virtually eliminates the dramatic head movements

otherwise required. There is also benefit in that the IMT does not require the use of a patient's hands. Dr. Primo stressed patient selection, training, and rehabilitation.

SPONSOR PRESENTATION

Judy Gordon, D.V.M., President, ClinReg Consulting Services, Inc., began the sponsor presentation by introducing the other presenters. She noted that none of the investigators who participated in the clinical trial have a financial interest in Vision Care. She then reviewed that the IMT is indicated for 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 also have adequate peripheral vision in the eye not selected, show an improvement of five letters on ETDRS visual acuity chart with an external telescope, and be willing to undergo a postoperative vision rehabilitation program.

Jeff Heier, M.D., Ophthalmic Consultants of Boston, began by giving an overview of end-stage macular degeneration. The IMT is an optical prosthesis which in combination with optics of the cornea constitutes a telephoto lens. There are two models, WA 2.2x and WA 3.0x, providing 2.2x and 2.8x magnification. As opposed to external telescopes, the IMT provides a wider visual field, allows natural eye movements, and has normal cosmetic appearance. It enlarges the retinal image and reduces the relative scotoma by projecting the image onto a larger portion of the normal functioning retina. The central five degrees may be partially or completely damaged in end-stage disease, and the IMT uses the central 50 degrees. The vertex difference present with external telescopes results in a narrow field of view. Dr. Heier demonstrated the differences using

scotoma mappings and field of view measurements taken from patients before and after implantation.

Stephen Lane, M.D., Associated Eye Care, Cornea/Anterior Segment, discussed the surgical procedure utilized. The IMT is larger than the standard IOL and requires at least a twelve millimeter incision. It is designed to be placed in the capsular bag, and the angulation of the haptics displaces the IMT posteriorly which keeps the bag taut, provides stability and centration, and improves clearance between the device and corneal endothelium. The anterior surface extends approximately half a millimeter through the plane of the iris.

There is a need to avoid corneal touch during insertion into the capsular bag; the surgical procedure results in average endothelial cell loss of twenty percent, which is similar to data for large incision cataract surgery.

The learning curve tends to last for the first three cases. Positioned correctly, both haptics should be inside the bag. Dr. Lane further explained the procedure and showed a brief video of the procedure.

Dr. Lane continued with a discussion of the study design of Protocol IMT-002. Twenty-eight centers participated. Patients were screened using an external telescope, and a gain of at least five letters was required for enrollment. In patients with better than 20/200 in one eye, implantation was done in the eye with poorer vision, and in those with worse than 20/200 in both eyes, the decision was based on the patient's experience with the external telescope. Patients returned for ophthalmic examinations and vision training at regular intervals. All participants are being consented for five years of continued follow-up.

Eligibility requirements included bilateral, stable, untreatable age-related macular degeneration (AMD); best corrected vision of 20/80 to 20/800; and adequate peripheral vision in the fellow eye. The baseline manifest sphere was limited to +4 to -6 diopters to exclude high myopes and high hyperopes. Those with ocular pathologies such as uncontrolled glaucoma were also excluded. Minimum endothelial cell density (ECD) of 1,600 cells per millimeter squared was required, but Vision Care has since proposed minimum ECD of 2,000 or an ECD grid based on age and life expectancy.

Distance and near vision were measured during all study visits using ETDRS charts. Quality of life was assessed using the visual function questionnaire–25 (VFQ-25) and a modified activities of daily living questionnaire. Specular microscopy was also performed, and images were analyzed by Drs. Henry Edelhauser and Bernard McCarey at a central reading center at Emory University.

The rehabilitation and training program was developed by experts led by Dr. Eli Pelli of the Schepens Eye Institute. It consisted of gradual vision practice exercises and emphasized five skills: localizing, fixating, scanning, tracing, and tracking.

The key safety and effectiveness endpoints were change in lines of best corrected vision, quality of life questionnaires, endothelial cell loss, and complications/adverse events.

Dr. Heier said that one of the 218 patients enrolled withdrew prior to surgery. Intraoperative complications resulted in eleven eyes not being implanted, leaving a total of 206 eyes. The complications were seven cases of posterior capsular rupture, two eyes identified as having choroidal detachment, one eye with choroidal hemorrhage, and one eye with loss of zonular support. With regard to the cases of choroidal detachment, there

was positive posterior pressure and chamber shallowing but no verified sign of detachment. The intraoperative complications did not result in vision loss.

Accountability for the 206 subjects was 97.5 percent at twelve months and 95.5 percent at 24 months. For the complete safety cohort it was 92.6 percent at 24 months. These levels of accountability are excellent considering the age of the subjects and the level of visual disability.

The mean age was 75 years. There was relatively even distribution of males and females. Most subjects were Caucasian. Mean baseline corrected distance vision was 20/312 but ranged from 20/80 to 20/800. The mean vision found in AMD treatment trials is typically in the 20/80 to 20/125 range.

Recent advances in the field of AMD provide new options for stabilization and possible visual recovery for patients with new onset exudative disease, but these options are not available for end-stage patients. The primary study endpoint was improvement in either distance or near vision of two lines or more at twelve months, and almost 90 percent of subjects reached this attained this outcome. Over 80 percent achieved improvement of three or more lines. The results were almost unchanged at 24 months. About 70 percent gained two or more lines in both distance ad near vision, and 50 percent gained three or more lines in both.

Looking at actual versus predicted visual improvement, patients came very close to the predicted results. About 50 percent met or exceeded the expected gain. Fewer patients met the gain expected with the external telescope.

The VFQ-25 is a validated quality of life questionnaire developed to measure the impact of vision problems. It has been established that a five to ten point change in score corresponds to a two or three line vision change. In the most relevant areas of the VFQ-25, patients demonstrated improvement of six to fourteen points. There was no effect of age, baseline vision, or IMT model on the change in scores.

There were significant improvements in questions five through nine, information not previously provided to the panel. IMT has demonstrated clinically significant benefits for end-stage AMD patients. Patients' vision and quality of life improved.

Dr. Stulting presented the safety findings. Two and a half percent of eyes lost two or more lines of best spectacle-corrected visual acuity. The gap between theoretical and actual performance was better for the IMT than for the external telescope. Since these differences exist, adjustment of the loss of lines by the theoretical gain is not a meaningful reflection of changes in vision for the study population; rather, the unadjusted visual acuity values are the most meaningful.

Following implantation there was a transient rise in intraocular pressure. Perioperative complications with an incidence of one or more percent were typical of large incision cataract surgery, although some cases of Descemet's detachment may have been due to the large profile of the IMT. Eight eyes developed non-visually significant posterior capsular pacification. Surgical capsulotomy has been performed in two implanted eyes. Postoperative adverse events were also typical of those associated with large incision cataract surgery with the exception of corneal edema, device failure, and inflammatory membranes on the IMT. Adverse events with cumulative incidence of five percent or more include iris transillumination defect and inflammatory precipitants,

which appeared in 24.8 percent of eyes in the early postoperative period and responded to dilation and steroid treatment. It is believed they are due to contact between the iris and the IMT, so dilation is recommended for three months after implantation.

The eight removals consisted of two device failures, four explants due to dissatisfaction of the patient, and two cases of corneal decompensation. The two failures were found to have cracks in the lateral wall which led to liquid condensation. Following additional physician training and modification of the manufacturing process the problem did not reoccur. Of those who were dissatisfied with the results, three complained of glare and bright light and the other experienced haze, loss of peripheral vision in the implanted eye, and loss of depth perception. In both cases of decompensation, the surgeon encountered positive vitreous pressure, iris prolapse, and shallowing of the anterior chamber during surgery. In one, one haptic was placed in ciliary sulcus. In both cases uneventful corneal transplantation and IOL exchange were performed.

As would be anticipated given the age of the study population, there were a number of nonocular adverse events, and there was consideration given to whether falls or fractures might have resulted from the IMT. It was determined that the falls were unrelated. The reported rate of falls for those with normal vision in the entire elderly population has been reported as four percent, and for those with low vision eleven percent. The observed rate among the study cohort was only two percent.

A standardized protocol and a central reading center were used to analyze ECD. In multicenter studies using a single reader precision of measurement of ECD varies from eight to ten percent.

The greatest reduction in ECD occurs between baseline and three months, which was anticipated given the incision size and configuration of the IMT. After three months the change between visits decreases substantially. Mean ECD approximated that of the cohort of 36 pseudophakic fellow eyes which had undergone cataract surgery prior to enrollment. However, the variation was greater for the IMT eyes.

Published literature reveals that endothelial cell loss was not substantially greater than for conventional cataract surgery, even modern small incision surgeries. Corneal edema and surgeon specialty were significantly associated with the change in ECD at three months. There also tended to be a greater loss for a surgeon's first case. Loss was less for those whose surgeries were performed by cornea trained subspecialists, which suggests that endothelial cell loss can be reduced through training and experience with anterior segment procedures. For a surgeon's first three cases, anterior chamber depth (ACD) had a linear effect on percentage change in ECD, but no effect thereafter. However, the predictive power of ACD was rather poor. Factors such as vitreous pressure and training seem to have a greater influence.

Surgeon training is critical. It is recommended that patients with higher greater ECD and ACDs be selected for each surgeon's initial cases. The rate of cell loss decreases with time, and a two percent gain in ECD was reported between twelve and eighteen months. The rate of loss continues to decrease during follow up, and this is consistent with acute surgery-related damage followed by endothelial cell migration and a return to a steady state rate of loss seen in the aging population.

Concerned about the rate of loss more than two years after implantation, a piecewise regression model was constructed assuming a change at three and nine months.

It is consistent with the known pathophysiology of cell loss after cataract extraction. Projections were made based on initial densities of 1,600, 2,000, and 2,500 cells per millimeter squared. Corneal decompensation occurs at around 500 cells per millimeter squared, so selection criteria can provide reasonable assurance of a clear cornea for the lifetime of the population.

A minimum ECD based on age and life expectancy should be used as a selection criteria. The risk of cell loss must be balanced with the significant improvements provided by the IMT.

PANEL QUESTIONS FOR SPONSOR

Dr. Grimmett wondered if the haptics were more stiff than a traditional IOL given that three or four percent ended up in the sulcus. Dr. Lane said they are indeed stiffer. Dr. Grimmett then asked about the measurement on the ultrasound slide, and Dr. Lane said it was taken from the center of the IMT to the endothelial surface. Dr. Grimmett then asked what the peripheral optic endothelial distance was, and Dr. Lane said it was 2.18 mm. Dr. Grimmett then asked for the mean ACD for the seven eyes on the slide, and the sponsor replied that it was 3.19 mm. He then asked why the other eyes were excluded. **Alan Sugar, M.D., Kellogg Eye Center, University of Michigan,** replied that the ultrasound biometric scope was obtained during the middle of the study and that it was a convenience sample.

Dr. Sunness asked about change over time in the visual acuity of the fellow eye. Dr. Gordon said the measurements had been made but were not included in the PMA. Dr. Sunness then asked about differentiating the effects of the vision training versus the

IMT itself. Dr. Bullimore said it was a challenge and said that the recommended labeling says the benefits of the IMT can be maximized with a rehabilitation program.

Dr. Weiss asked why some patients had hyphema and also asked whether the stiffness of the haptic and resulting sulcus placement might be associated with the cyclodialysis and seen in two patients as well as bleeding. Dr. Lane suggested the hyphema was a result of the large incision. He said it was possible the stiff haptics had resulted in cyclodialysis but thought it was complicated by other factors. However, he noted that there were cases without complications in which one haptic was not placed in the bag.

Dr. Weiss next asked why the sponsors used needling rather than YAG capsulotomy on two patients with visually significant PCO. Dr. Lane said that in one of the cases there was not adequate papillary dilation. Dr. Weiss inquired further about a recommendation made that YAG capsulotomy be used to dissect adhesions. Dr. Lane said he did not think that had been attempted and would be quite difficult. He said that it would depend on the extent of the adhesions. Dr. Gordon added that all of the labeling presented was proposed draft labeling and would be revised.

Dr. Palta asked about continued difficulty with reading newspapers, and Dr. Bressler said that was the most difficult task on the VFQ and that even those with 20/80 vision prior to implantation would not be expected to be able to accomplish it without at least some difficulty. Dr. Palta asked whether the final model referred to was the piecewise linear mixed effect model and also asked about the exponential model. Dr. Gordon replied that the first reference in the slides was not to the piecewise regression

model. **Henry F. Edelhauser, Ph.D., Emory University,** said the modeling had not taken into consideration the increase in peripheral endothelial cell densities.

Dr. Heuer asked whether the sponsor had attempted to assess the degree to which cataract removal alone contributed to the improvements in vision. Dr. Bullimore said that one entry requirement was no visually significant cataract and that their preoperative visual acuity using the external telescope was pretty similar to what they achieved with the IMT.

Dr. Huang asked whether any patients had posterior capsule rupture after implantation given that the final tabulation indicated ten patients with rupture while seven were excluded from implantation due to posterior capsule rupture. Dr. Gordon said they would answer the question after they reviewed the data. Dr. Huang then asked for explanation of patients' indications of significant improvement of near vision. Dr. Bullimore said that it was not a multifocal device and that the patients would function like any other presbyopic patient using reading glasses or bifocals. Dr. Huang asked whether it was measured binocularly. Dr. Bullimore responded that the VFQ was concerned with habitual, binocular vision, including with corrective lenses.

Dr. Bressler asked for a definition of "no active CNV" as an enrollment criterion. Dr. Heier said there had to be no signs of active neovascularization or bleeding within the past six months and clarified active to mean no fluorescein leakage. Dr. Bressler then asked about the follow up and vision outcomes for the eleven eyes not implanted. Dr. Gordon said they were followed as long as they were willing to come back and that there was no loss of vision from baseline. Dr. Bressler next inquired whether last observation carried forward was used for the thirteen subjects lost prior to twelve months. Dr.

Gordon said that observed data was used in all analyses and that the high accountability lessened the importance of the missing data for those patients. Dr. Bressler asked for the most recent data on those thirteen, and Dr. Gordon said it was included on the slide showing loss of lines of acuity.

Dr. Ferris asked for clarification of his confusion regarding clear lenses given that the eligibility criteria state there must be evidence of cataract. Ms. Thornton asked the sponsor to defer the answer until later so that the FDA's presentations could go forward.

FDA PRESENTATION

Don Calogero, M.S., Biomedical Engineer, Intraocular and Corneal Implants Branch, began with a description of the two models of the device. The anterior surface of the IMT protrudes about 0.6 millimeters into the anterior chamber. Due to the magnification, retinal luminance is reduced by 0.7 for the 2.2x and 0.9 for model 3.0x. The standard battery of preclinical tests was performed. FDA has no concerns remaining regarding the preclinical testing. Mr. Calogero introduced the rest of the PMA review team.

Bernard P. Lepri, O.D., M.S., M.Ed., Clinical Reviewer, Vitreoretinal and Extraocular Devices Branch, presented the analysis of the critical clinical outcomes. He read the proposed indication: 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; and have adequate peripheral vision in the non-operative eye. He

then discussed the study. The primary effectiveness endpoint was improvement of two lines or more of best corrected distance or near vision in 50 percent of eyes at 12 months, and the secondary measure was performance on the two quality of life surveys. The primary safety endpoint was mean ECD loss of less than or equal to 17 percent at 12 months, and preservation of best corrected visual acuity was another.

Dr. Lepri reviewed the data on endothelial cell loss. For the ten percent of eyes with the greatest decrease, there was a 60 percent loss for the implanted eyes versus only 12.5 percent for the fellow eyes. The fellow eyes show relatively constant ECD. The sponsor presented no morphometric data. In making its recommendations the panel should also consider surgical order, ACDs of less than 3 millimeters, and surgeon specialty. Age is also an important consideration given increasing life expectancies.

Corneal edema becomes possible at ECD of less than or equal to 800 cells per millimeter squared, so FDA looked at the number of eyes that would deteriorate to ECD of less than or equal to 1,000. At two years, 11.1 percent of eyes are projected to be at or below that level; at three years, 17.6 percent; and at four years, 22.7 percent.

ACD is related to ECD loss due to the increased potential for surgical trauma as well as the proximity of the IMT to the endothelium following implantation. While early post-op losses attributed to shallow ACD do not appear to contribute to the chronic losses, they are permanent and thus potentially meaningful. Eyes with ACD less than three millimeters have the greatest losses at all time periods. ACD between 3 and 3.5 millimeters showed clinically significant less ECD loss, and the same held true for eyes with ACD greater than 3.5. Also, both the patients who experienced corneal decompensation in subsequent transplant had ACD of less than three millimeters.

Though the IMT was designed for two millimeters of corneal endothelial clearance and the selection criteria specified minimum ACD of 2.5 millimeters, no data was presented to demonstrate the suitability of the proposed minimum ACD.

Furthermore, there is evidence that sulcus placement of the haptic moves the device anteriorly, thus increasing the risk of corneal touch. Also, one eye was reported to have posterior capsular opacification (PCO) at 18 months, and two had visually significant PCO at 24 months. A needling procedure rather than YAG capsulotomy was used to address these two cases. The proposed labeling includes instructions for using a YAG through the periphery of the device, but this would require more bursts, more energy to the eye, and thus increase the risk of retinal detachment.

Turning to clinical effectiveness, mean preoperative visual acuity data indicates that most study subjects were categorized as legally blind. There are significant fluctuations in repeated measures of acuity in macular degeneration patients. 90.1 percent of implanted eyes were reported to show improvement of two lines or more in either distance or near vision; for refractive lasers and phakic IOLs such a change denotes a clinically significant change in visual function, but these eyes are not diseased or considered low vision. Repeatability coefficients for young normal patients are significantly smaller than those found in a study of low vision and uncorrected normal vision subjects. Data from the PMA indicate that those with severe and profound vision loss showed greater than three lines improvement.

Comparing predicted postop acuities with those actually reported, the IMT resulted in somewhat better distance acuities, but the near acuities did not measure up to the predicted values. The safety and effectiveness for visual acuity are based on

unadjusted baseline acuity rather than on that predicted based on the magnification. There was no data on how much of the improvement was a result of the cataract removal alone. Also, the preoperative acuity measurements were not adjusted.

Items five through nine of the VFQ deal with independent mobility. Mean scores were provided, but FDA requested frequency analyses for each rating within each category assessed. The number of subjects reporting extreme difficulties decreased by one year, but those reporting little and moderate levels of difficulty increased.

The rehabilitation program was directed by family members and did not use any direct performance measures, though progress was checked at scheduled visits. Studies have shown that vision rehabilitation with specific individualized goals directed by specialists yields a high rate of sustained success. Studies also show that those with low vision are at increased risk of falls. Eight fall-related adverse events occurred during the trial. Training by a low vision specialist (Orientation & Mobility Specialist) should be required.

It is proposed to use the IMT both monocularly and binocularly, but binocular use presents serious concerns, including noncorrespondence of overlapping fields, severe field restriction in the dominant eye, motion discrepancies, and possible suppression of the fellow eye. No symptoms of discordant motion information were reported, and this suggests there is suppression of either the IMT image or the entire fellow eye. Since the IMT has more prominent motion stimulus, it is more likely the fellow eye is being suppressed. The result would be a severely constricted visual field.

Hollington T. Lu, M.S., M.A., Mathematical Statistician, Division of Biostatistics, Office of Surveillance and Biometrics, began the statistical review, which

focused on the 24 month database. He showed a scatter plot of the ECD counts over time, both for IMT and fellow eyes. ECD percent loss from baseline to three months is 20 percent. The yearly average loss is 5.4 percent. Looking at ECD loss of more than ten percent, at eight months 59 percent of IMT but only five percent of fellow eyes has such losses. No fellow eyes had more than 20 percent loss, but 12 percent at three months and 19 percent at 24 months of IMT eyes had at least 50 percent loss. Turning to ECD and surgical order, the sponsor states that ECD has a linear effect on ECD percent change from baseline to three months, but not after that, and surgical order did not show statistically significant difference.

Yao Huang, M.S., Mathematical Statistician, Division of Biostatistics, Office of Surveillance and Biometrics, noted that at baseline ECD values were similarly distributed for both eyes. For the fellow eye it is roughly constant, but for the IMT eye there is a large drop in the first three months, and ECD may continue to decrease at a lower rate. A mixed effect model was used to analyze the ECD data. Mean baseline ECD was 2466.89. IMT eyes dropped 169.81 per month for the acute period and 9.83 units per month during the chronic period. The fellow eyes lost 6.59 units per month, but that number is not statistically different than zero.

The question when ECD would fall to 1,000 cells cannot be answered because no data is available, and data extrapolations should be avoided as there is no certain knowledge regarding the pattern of ECD loss. However, FDA projected the mean ECD at four years by assuming the chronic linear trend continued. By the mixed effect model at the end of year four projected mean ECD count for IMT eyes would be significantly lower than for fellows. Quartile analysis was also performed to further look at the

relationship between baseline ECD and long term ECD projection. There was no statistically significant difference in either age or ECD across the strata of baseline ECD.

According to the sponsor's data, a subject with baseline ECD of 2,500 and ACD of 2.5, the probability that ECD will be lower than 1,000 is .149, and for one with ECD of 1,600 and ACD of 2.5, the probability is .644.

For IMT eyes, ECD decreases throughout the study, and the rates of loss in both the acute and chronic periods are significantly different than zero, and in both periods the rates are significantly different between the IMT and fellow eyes. This suggests there is a significant treatment effect.

Dr. Weiss asked about the slide which showed that because of the magnification, an improvement of less than 1.4 lines or 2.3 lines of acuity would actually equal a loss of greater than 2.0 lines of acuity. She questioned what percentage of patients who seemed to have improved, actually got worse.

Bruce Drum, Ph.D., Division of Ophthalmic Devices, acknowledged that FDA was also troubled by that but that the sponsor had not provided the information. Dr. Weiss then asked whether patients may have perceived an improvement that could not be measured. Dr. Drum said that using adjusted acuity provided more of an indication of device effectiveness but noted that patients were more concerned with using the preoperative acuity.

Dr. Palta asked about use of an exponential or log scale. Ms. Huang said that it was actual ECD count, not a log scale. Dr. Palta noted that some of the literature fits either the exponential or double exponential, which would result in slightly lower percentages of ECD loss. Ms. Huang said the results had been compared with the

literature and that the parameter estimates were close, even the extrapolation. Dr. Palta asked whether the random effects were assumed on the intercept or slope, and Ms. Huang said yes. Dr. Palta asked whether the percentages showed were from the same model, and Ms. Huang said they were and added that based on the model she had predicted the ECD count for each patient. Dr. Palta then asked about the confidence interval or precision for the predictions. Ms. Huang responded that as the sample size was relatively large, there was pretty high precision in parameter estimation, but that the distribution of ECD counts itself was rather wide and that there was a high proportion of eyes with counts of 1,000 or lower among IMT eyes.

Dr. Ferris returned to the issue of expected improvement and suggested it would have been surprising if all eyes had achieved the theoretical improvement given the condition of the eyes. Dr. Drum said the other factor was possible measurement error in that the preoperative measurement may have been on a good day and thus better than their average acuity. Similarly patients who showed strong improvement may have had low preoperative measurements. Dr. Ferris then asked whether multiple training sessions might improve one's ability to perform well on some of the tests, and Dr. Drum agreed with that view. Dr. Lepri noted that another possible explanation for the larger increases in acuity may have resulted from the fact that a majority of the patients had cataracts prior to surgery.

Dr. Szlyk asked whether visual function on the VFQ was similarly divided by visual acuity level. Dr. Lepri responded that those with severe and profound vision loss showed larger proportional improvement on the VFQ.

Dr. Weiss asked for clarification of the level of cataract and whether visually significant cataract was an exclusion criterion. Dr. Lepri said the indication required patients to have cataract, and the sponsor indicated that they had misspoken regarding exclusion of visually significant cataract. Dr. Lepri said that over 90 percent had nuclear cataracts but did not recall data on the degree of nuclear or cortical opacification and agreed that the absence of that data made it impossible to determine the effect of the device versus that of the cataract removal.

Mr. Bunner asked about the unknown problems of examination and treatment of IMT implanted eyes. Dr. Lepri responded that FDA was concerned about the use of devices typically used to examine the retina but noted that the sponsor had addressed some of those concerns in stating they would dilate the pupil and use a Volk lens with the slit lamp. Other methods were not addressed.

Dr. Mathers asked whether laser treatment of the retina would be precluded, and Dr. Lepri said it was unknown given the lack of data.

PANEL, PRIMARY REVIEWS

Dr. Grimmett began his review by noting that other studies tracking corneal endothelial health had 500 or more eyes whereas the current PMA began with 206 and had only around 150 at 24 months. Eight eyes had PCO. Two required a needling procedure, and Dr. Grimmett pointed out that most practicing ophthalmologists have no idea how to do a needling. A YAG can't be done through the optic of the IMT, and a circular YAG around it is suggested, but in animal models it required significantly more bursts than a standard capsulotomy. There is a question whether the high number

required increase the risk of retinal detachment. Furthermore, a circular capsulotomy may result in a very large vitreous floater.

Transient IOP elevations seen in a quarter of patients are likely related to viscoelastic, and sulcus placed haptics can narrow or close the angle. However, gonioscopy data was not included with the application. Pigment deposits on the IMT may be a sign of chronic iris chafing with possible pigment dispersion syndrome. Several routine eye care issues, including angiograms, peripheral retinal exam and laser, and argon laser, are negatively affected by the IMT. And it is unknown whether retinoscopy or optical coherence tomography (OCT) is possible in an IMT-implanted eye.

Turning to effectiveness, Dr. Grimmett noted that the patient, with family assistance, was largely responsible for implementing the rehabilitation program. Investigators noted that rehabilitation was a key factor to a successful outcome, and some said it should be mandatory. Dr. Grimmett advocated it as a labeling requirement.

Moving to the corneal endothelium, Dr. Grimmett noted that the IMT was similarly proximate to the cornea as an angle supported phakic IOL. No data on optic endothelial distances was presented in the PMA. Ultrasound data presented today showed a central distance of 2.54 and peripheral distance of 2.18, but the range of ACDs was not known. Furthermore, the seven eyes presented are not likely to be representative of the entire cohort. It is important to know where the IMT sits in eyes with the narrowest ACDs. Two published cases with one haptic in the sulcus and the other in the capsular bag had distances similar to the first generation angle supported phakic IOLs, which were unsafe and led to marked endothelial cell loss. Two corneal transplants were performed in the study, and both eyes had ACDs of less than three millimeters and a

sulcus haptic. Based on the limited data available, the IMT endothelial distance is barely sufficient and some eyes probably have dangerous proximity, and Dr. Grimmett recommended that ultrasound data be provided.

The FDA's model for endothelial cell loss is supported by published studies of large incision cataract surgery, but the sponsor's three slope model is not supported by literature, and there is no morphometric data to justify the choice of breakpoints. It is important to know whether the loss is due to remodeling due to surgical trauma or due to a chronically stressed endothelium. A critical deficiency in the PMA is the total lack of morphometric data, which is known to be a better indicator of endothelial health than ECD data, and which could ensure that the coefficient of variation and percent hexagonals return to baseline levels in a reasonable period of time.

There were also no measurements of the peripheral endothelium, and the superior cornea in particular may act as a reserve for remodeling but may also be damaged by the large superior incision required for implantation. Similarly, in spite of its relevance to corneal endothelial function, pachymetry was neither routinely measured postop nor reported in the PMA.

Looking at the exclusion criteria, there were relevant confounding factors such as diabetes and contact lens use that were not specifically excluded. Chronic inflammation, a known factor in endothelial damage, is caused by the IMT and is greater than for standard cataract surgery, and Dr. Lane reported it was the most notable complication in the phase one trial. Based on inflammatory and pigment deposits on the IMT, chronic inflammation cannot be ruled out as a cause of ongoing damage to the endothelium.

Turning to ACD, there was a trend of higher cell loss in shallower chambers, and it would be prudent to exclude narrow ACDs. The study closely matched known loss rates for both pseudophakic and unoperated eyes.

The acute ECD loss in the study was 21 percent compared with 12 percent for large incision cataract surgery, and the yearly chronic loss was around six percent compared with 2.5 percent for large incision cataract surgery. Furthermore, the chronic loss for IMT eyes was ten times the rate for unoperated eyes.

Looking at minimum cell density to ensure corneal clarity, a 60 year old patient would need a preoperative count of 3,984 in order to die with a count of 800, the threshold identified for potential corneal edema, 22 years later, but the average 60 year old will only have around 2,700 cells. After age 70 it might be expected to find patients with high enough counts that ECD will not fall below 800 before death. However, merely using the mean will not adequately describe adverse corneal outcomes that may affect a significant number of eyes. If the chronic loss rate does not slow down, an epidemic of corneal edema may result not long after implantation. Even under the best conditions, that is, entry cell count of 2,500, seven to fifteen percent of eyes may be at risk of corneal edema at year four.

Returning to the lack of morphometric data, if the data turn out to be consistent with an unstable endothelium the device would be unsafe and not approvable. If the data is consistent with ongoing remodeling, then it would be conceivable that the chronic rates would slow down.

Dr. Grimmett suggested restricting the device to ACD of 3 millimeters or more, minimum entry cell count of 2,500, and minimum entry age of 75, or alternatively

creating a sliding scale of baseline cell counts for given ages based on life expectancy tables. New surgeons should start with deep anterior chambers. Labeling should state that the device is unsafe when placed in the sulcus. Future specular photographs should include a peripheral measurement, particularly from the superior cornea.

Dr. Bressler began his review by acknowledging that the sponsor had attempted to address a major public health problem. Study design limitations include the lack of controls, which eliminates the possibility of determining the visual acuity improvement due to the IMT itself rather than to removal of the cataract and rehabilitation. The VFQ results are also limited in that scores can improve over time even with no treatment or the improvement could be due simply to cataract removal and rehabilitation. In the absence of controls, the results were not overwhelming enough to be able to conclude anything about effectiveness.

Another problem is that the analysis omitted the eleven eyes which did not have successful implantation. While the sponsor stated they were giving the results of successfully implanted IMTs, the protocol merely said they would look at the results of those undergoing implantation. Another limitation is the lack of twelve month follow up for the eight eyes from which the device was eventually removed. Dr. Bressler suggested it would important to look at the effect on the overall data set if those lost to follow up had bad outcomes.

As to the modified activities of daily living questionnaire, there was no explanation of how it had been modified or validated. Dr. Bressler was also concerned whether PCO was systematically looked for in follow up. There was also a lack of information on possible vestibular problems and on total additional procedures

performed, which could have been compared to historical controls of how many are done following cataract surgery.

A seventeen percent ECD loss was chosen a priori at the start of the trial, and it was not met. There was also insufficient information on YAG capsulotomy. Dr. Bressler also expressed serious concern over the theoretical risk related to magnetic resonance imaging (MRIs) and suggested further consideration of another model that would avoid that issue given the uncertainty that the indicated population would require an MRI at some time following implantation. He also suggested that the five point change in VFQ score might be somewhat low to be clinically significant.

The sponsor's recommendation that no treatment for AMD be required for the past six months may be problematic given new treatments for choroidal neovascularization which might benefit patients. It is unknown whether fluorescein angiography can be performed and reliably interpreted to identify disease. There was a lack of information on the seemingly changing definition of macular degeneration used as well. Also, it would be helpful to have information on how the near visual acuity was calibrated.

Dr. Brilliant began with a discussion of age-related macular degeneration. Magnification is used to help patients function, and there are four approaches: relative size, projection, relative distance, and angular, which is use of a telescope. The magnification used is determined based on the patient's own goals. For general goals the target acuity is 20/40 or 20/50. The IMT is a Galilean refracting telescope, and the advantages over external telescopes are cosmetic and lack of the weight problem associated with prolonged use of an external scope. Dr. Brilliant was concerned that

only sixty percent of the subjects achieved a doubling of their acuity using the IMT. Also, if a patient's vision decreases such that more magnification is needed, additional surgery, with the costs and risks entailed, may be required.

Apparently subjects' specific visual concerns were not considered in candidate selection. One problem is that the questionnaires showed distance vision activities improved less than general or near vision, but a telescope is mainly intended to improve distance vision. Another concern is that subjects were apparently not shown external telescopes with greater than 2.2x magnification prior to implantation which may have provided better results. Dr. Brilliant stated that in reality only patients with acuity from 20/80 to 20/140 would truly benefit from the IMT based on the two magnifications available. The telescope may improve acuity in other patients, but not necessarily to the extent that the person can function on certain tasks.

Turning to near acuity, the target would again be in the range of 20/40 to 20/50 based on the size of standard print. However, reading individual optotypes on a chart is much easier than reading words and sentences. When the dioptric power of the telemicroscope required for reading is determined, it is apparent that the same power could be produced with a pair of reading glasses without the telescope. Further, the patient would probably adjust better, and the field of view would be much larger than in an equivalent power telemicroscope.

The sponsor argued that because of the reduced central vision of the study subjects less than the theoretical improvement should be expected, but Dr. Brilliant stated that patients should and do improve as expected. When they do not, certain factors should be looked at to determine why. Dr. Brilliant was uncertain why the eye with

worse acuity was implanted if best corrected vision was better than 20/200 in either eye. Assuming the fellow eye had enough peripheral field for mobility, maximum benefit would be achieved by implantation in the eye with better acuity. No binocular or binocular examination was performed prior to surgery, and there was no evaluation of whether the fellow eye would be suppressed when using the telescope as needed for mobility.

The telescope is focused for three meters rather than optical infinity, so to see at a greater distance a minus concave spectacle lens would be needed, and it would decrease the magnification and thus the visual acuity. Dr. Brilliant questioned how much astigmatism would be enough to exclude a potential candidate.

The IMT may be statistically successful for general vision improvement and may help those with 20/70 to 20/140 acuity

PANEL DISCUSSION

1. Please discuss the following regarding endothelial cell density:

a. The primary safety endpoint for this study was mean ECD ≤ 17%. The sponsor reported mean percentage change in ECD from baseline to 12 months of 25.3%. Does the panel believe that the study design has provided sufficient data to address the long-term ECD safety issue associated with this device?

The panel generally agreed that there was neither enough data nor enough analysis of the data provided and that the sponsor did not reach the established safety endpoint. One panel member pointed out that FDA should work with industry to define endpoints as this seems to be a recurring problem and also that ECD alone may not tell the entire story as some patients with a count of 500 cells still have very clear cornea. Some panel members

suggested moving forward with an increased age requirement and increased anterior chamber depths until there is more data on those currently enrolled.

b. Please discuss whether these data provide a reasonable assurance of the safety of the IMT for the 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 endothelial cell density at entry**
- **age**
- **other**

One panelist said that if the panel thought there was reasonable efficacy that these criteria could be modified to mitigate safety concerns. One panel member said there should be more studies first. Another panel suggested that perhaps data on survival of eyesight should be used instead of life expectancy due to the potential effect of other eye problems. One panel member worried about the learning curve in the larger population of surgeons.

2. With regard to the long-term follow-up of eyes with the IMT:

a. 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.

Panel members did not feel there was reasonable assurance of safety in doing a YAG procedure given that it had not been performed during the course of the study. One panel member was unsure how successful needling would be. Another panel member expressed confidence in the ability of ophthalmologists to figure out how to do a capsulotomy on these patients.

b. Please discuss your concerns, if any, regarding posterior segment examination and treatment of eyes with the IMT.

Panel members expressed concern regarding the risk of patients developing choroidal neovascularization and that the ability to do angiography would be limited by the device. Another concern identified was how to approach a retinal detachment in these patients. Limitation of future treatment options is a significant issue. One panel member suggested adding diabetes as an exclusion factor.

3. The proposed safety and effectiveness criteria for visual acuity are based on unadjusted preoperative acuity rather than on acuity predicted from the magnified postoperative retinal image.

a. Please discuss whether the unadjusted preoperative acuity baseline is adequate for evaluation of safety and efficacy of this device.

b. Please provide any recommendations on what additional analyses are needed, if any, to evaluate visual acuity measures of safety and effectiveness.

Panel members expressed concern regarding the lack of controls and the lack of information on the cataracts present preoperatively. One panel member suggested there should be stratification of the results based on whether the implanted eye had better or worse acuity, analysis of any preoperative improvement as a result of the minimal rehabilitation training done preoperatively, and an analysis of the visual acuity change in the unoperated eye which might act as a control. Another member suggested looking at the refraction or correction used for the baseline visual acuity. Several panel members were in favor of using adjusted preoperative acuity rather than the magnified adjusted vision. One member pointed out that the loss of luminance with the IMT would reduce vision in macular degeneration patients. Some panel members argued that using the fellow eye as a control would be potentially flawed. One panel member suggested that

some data might be gleaned from fellow eyes that also underwent cataract surgery and IOL implantation.

4. In the IMT trial, the rehabilitation program was implemented by the subject with assistance from the family. Professional orientation and 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.

b. If not, please discuss modifications to the vision rehabilitation program recommended for patients that receive the IMT.

There was agreement among some panel members that rehabilitation should be required both pre and post-op. One panel member did not feel comfortable requiring something that had not been demonstrated to be helpful. One panel member was in favor of requiring professional rehabilitative services but worried about the availability of those services. The FDA clinical reviewer. Dr. Bernard Lepri, clarified that their concern was with orientation and mobility training following surgery due to the safety concerns with the elderly patient population.

5. Regarding the rehabilitation training program to teach IMT subjects to use their implanted eyes for central vision tasks and their fellow eyes for peripheral vision tasks:

a. The sponsor has provided no direct performance measures showing that subjects can learn to shift binocular suppression from one eye to the other at will. Please discuss whether 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.

b. Please provide any recommendations you may have for modifying the instructions for dealing with binocular rivalry and suppression problems.

One panel member said it would depend on the patient and that it would be wise to identify those that would not be able to shift binocular suppression from one eye to the other prior to implantation. Another member suggested there were ways to study this by

making the fellow eye a component of future studies. One member suggested a longer trial period with the external telescope along with monitoring of patients' progress with the trial. The chair acknowledged that patients' use of central versus peripheral vision would be complex. One panel member thought the issue had been indirectly addressed to some degree by the activities of daily living questionnaire. Another panelist addressed the issue of double vision and thought the subjects must be closing one eye when reading given the difference in acuity between the two eyes.

6. The sponsor proposed the following indication for 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 with bilateral, stable central vision disorders resulting from age-related macular degeneration as determined by fluorescein angiography, and evidence of cataract.**
- **Distance BCVA between 20/80 and 20/800, 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 ETDRS chart in the eye scheduled for surgery using an external telescope.**
- **Show interest in participating in a postoperative visual rehabilitation program.**

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. If not, please comment on whether your concerns can be mitigated by modifying the following:

a. Age
b. Preoperative VA
c. Definition of minimal acceptable peripheral vision
d. Type of AMD
e. other

Some panel members agreed that the age should be increased. One panel member wondered about plasticity and the ability of older patients to adapt to the device. Other panel members expressed concern about predicting how long individual patients will survive. The Chair stated that life expectancies were increasing and might increase dramatically in the coming years.

Panel members thought that those with lower preoperative visual acuity might be more appropriate but also acknowledged that those with better preoperative VA would be much more likely to improve to a level of functionality, although not many actually did. One panel member reiterated his point that those with very low VA would not be improved to a functional level with the magnification of the IMT and thought such patients should be given the opportunity to try external scopes with magnification more in line with their level of VA. Another panel member suggested that any improvement might be satisfactory for such patients and that all patients should be given options other than the invasive surgery required for the IMT. One panel member suggested that some of these factors would be more appropriately addressed as part of informed consent and pretreatment evaluation. An FDA representative stated that since subjects were not given the option of telescopes with very high magnification that their level of satisfaction was not reflective of the options. A panel member said it is hard to predict when choroidal neovascularization would reactivate and that bilateral geographic atrophy would be the least problematic.

Regarding peripheral vision, the FDA representative clarified that they were asking about patient selection. Some panel members said it was difficult to assess peripheral vision in those with central vision loss but felt there should be a general feeling that a patient has around thirty degrees in each quadrant. One panel member suggested a test could be devised to assess functional ability related to peripheral vision as opposed to the actual dimensions of the field.

OPEN PUBLIC HEARING

No members of the public came forward to speak.

FDA CLOSING COMMENTS

The FDA had no closing comments.

SPONSOR CLOSING COMMENTS

Dr. Gordon said that the slides presented by Dr. Grimmett showing anterior segments on ultrasound biomicroscopy (UBMs) were of a previous model of the device. She expressed regret that the sponsor had not had an opportunity to write responses to the panel questions.

Dr. Stulting addressed the issue of the effect of cataract surgery on vision improvement. He stated that the lenses of the patients were clear enough to allow for examination of the retina and fluorescein angiography and that none of the patients had sufficiently advanced cataracts that cataract surgery alone would have been recommended. Also, thirteen fellow eyes also had cataract surgery, and the average gain was only one line of acuity. Randomization would be difficult to achieve. Regarding the outcome of eyes in which implantation was aborted or the device removed, Dr. Stulting said that mean postop acuities were within .02 logMAR units of the preoperative values; eight were within one line; two lost two or more lines; and two eyes gained two or more lines.

Regarding the issue of theoretical improvement, Dr. Stulting stated that the increased acuity and functional vision were real and that patients were not concerned whether they achieved the theoretical improvement. Advantages of the IMT include increased visual field, ability to scan without moving the head, and that a patient's hands are not required to support the device. The data supports approval under limited

circumstances, which would allow for collection of long term data to address the questions addressed.

Dr. Heier said that examination of the retina could be done through the telescope or the periphery and that retinal detachment could hopefully be treated using peripheral viewing. With regard to patients with lesions, the sponsor does not advocate use of the device in patients being treated with ranibizumab.

VOTING

Ms. Thornton read the voting options. Dr. Bressler moved that the device application be found not approvable. Dr. Grimmett seconded the motion.

Dr. Bressler appreciated the data provide on the missing subjects but thought those who underwent implantation needed to be looked at in depth to see if the ten percent vision loss safety margin was surpassed. He said there was not enough information to establish effectiveness. As to safety, he was concerned that the ECD loss was greater than what was thought to be safe.

Dr. Grimmett was most concerned with the chronic cell loss. He thought it was likely due to remodeling and would decrease over time but said there was insufficient data to know. He hoped morphometric data could be analyzed to determine whether patients returned to baseline and that it might allow the sponsor to justify their choice of break points.

Dr. Palta felt the discussion of mitigation of risk had altered the risk benefit ratio enough to make the vote somewhat difficult.

Dr. Ferris said that without controls he could not know the magnitude of the benefit. He wanted another voting option whereby the sponsor could do limited marketing and a concurrent randomized clinical trial.

Ms. Thornton stated that in the event of a vote of not approvable the panel would be asked what was necessary to make it approvable. Dr. Ferris expressed hope that the concept would not be abandoned due to the high cost of conducting another clinical trial.

Dr. Weiss said there was not valid scientific data showing reasonable safety and efficacy. She asked the primary reviewers to identify data that might be gleaned from the current study to establish effectiveness.

Dr. Bressler said they needed to look at all the missing data to make sure it does not increase the loss of vision beyond the established safety threshold. He said it would be difficult to address issues with the VFQ and the visual acuity information without controls.

Dr. Grimmett said his primary concern was with safety, not effectiveness.

Ms. Niksch said it was unfortunate that the sponsor had not had an opportunity to fully address the comments of the primary reviewers.

Dr. Heuer asked whether the panel could recommend the device be approvable pending morphometric data, and Dr. Mathers said they were supposed to go on available data.

Dr. Weiss asked whether the device could be voted approvable with the condition that morphometric data be obtained from existing photographs. Dr. Eydelman said it would be difficult to make such a recommendation pending data that wasn't collected, Whether or not the sponsor has it or not, the FDA has not been privy to it. She stated

that if would be helpful if the panel made a recommendation pending data that we know exists.

Dr. Haik asked if the technology would simply disappear if it was not approved. Ms. Niksch clarified that it would be a long process to design a randomized control trial.

Dr. Eydelman said that if the panel voted a recommendation of not approvable, they could then address what data they think the sponsor should provide to bring the application into approvable status.

Dr. Huang said that the device was efficacious given that it is equivalent to using an external telescope and that the safety issues were related to the surgery, which was not much worse than previous cataract surgery.

Dr. Mathers called the vote. The motion passed with ten supporting and three voting against the motion. The Chair did not vote.

FINAL PANEL COMMENTS

Ms. Thornton stated for the record that Dr. Ferris had to leave and would not be available for final comments.

Dr. Palta felt that with the conditions discussed the benefits would just barely exceed the risks.

Dr. Grimmett said that the available data did not support the safety of the device. He thought the sponsor could garner morphometric data from existing photographs, lending credibility to the theory of prolonged remodeling and showing appropriate cell loss rates.

Dr. Weiss said the scientific evidence presented did not show reasonable safety due to the endothelial cell loss rate and that the lack of data on confounding variables meant that reasonable efficacy also was not demonstrated. She hoped the complete data set would be made available.

Dr. Heuer said the safety issue was a major problem and thought the morphometric analysis as well as a more thorough understanding of the chronic cell loss was needed.

Dr. Edrington was also concerned with the data on the endothelial cell counts.

Dr. Szlyk felt they had sufficient data to approve the device with certain conditions.

Dr. Haik said he very much wanted to approve the device but that based on the evidence presented and the opinion of the primary reviewers he had supported the motion.

Dr. Brilliant did not feel the safety and efficacy data was sufficient.

Dr. Sunness regretted that she had to support the motion. She was primarily concerned with the safety issues, but with regard to efficacy she wanted to see data on the fellow eye.

Dr. Bressler agreed that the scientific data provided did not establish safety and efficacy. He felt there was a need for controls and regretted that had not been known from the start. He thought the design would have been okay had there been an overwhelming response.

Dr. Burns was primarily concerned with the safety but also thought it would be nice to have reassurance that a retinal exam could be performed in these patients. In terms of efficacy, he was swayed by the fact that the patients were satisfied.

Dr. Huang voted against the motion because he did not think extrapolation of the existing data could be compared with the life table analysis.

Dr. Mathers was most concerned with the safety issue. He thought it was somewhat efficacious and hoped the sponsor would be able to make the device approvable.

Ms. Niksch pointed out that the study was conducted under an approved IDE after negotiations with FDA. She commended the sponsor for their innovative device and hoped for continued collaboration to bring the device to the market.

Mr. Bunner said that with informed consent he thought the device could be a choice for consumers.

Dr. Mathers asked the panel to give some guidance to the sponsor and FDA on how the issues of safety and effectiveness raised by the panel may be addressed in future submissions to the Agency.

Dr. Burns hoped the sponsor could limit the age range and resubmit data without having to undergo another trial.

Dr. Haik expressed his concern as to why neither morphometric data nor multiple specular micrographs were taken. He also thought the sponsor should have been accounted for the possibility of future treatment options.

Dr. Sunness said that patients with bilateral geographic atrophy with choroidal neovascularization were a good group and that people with geographic atrophy in one eye

and cytomegalovirus (CMV) in the fellow eye were not. She also thought it would be reasonable in patients with large disciform scars unlikely to be eligible for treatment.

Dr. Bressler expressed concern over the development of efficacy data due to reported that are coming out regarding changes in the NEI-VFQ. He suggested that this needed to be taken into account in the AMD population. Also the emerging information visual acuity changes related to scars following cataract surgery is to be noted. He suggested that maybe a small controlled trial could be done to establish efficacy.

Dr. Mathers hoped that panel members might make further suggestions at a later time.

ADJOURNMENT

Dr. Mathers adjourned the meeting at 5:28 p.m.

I certify that I attended this meeting of the Ophthalmic Devices Advisory Panel Meeting on July 14, 2006, and that these minutes accurately reflect what transpired.

_____

Sara M. Thornton
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

_____

William D. Mathers, M.D
Chair

Summary prepared by

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