U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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OPHTHALMIC DEVICES PANEL

105TH MEETING

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FRIDAY
MAY 23, 2003

The Meeting was convened in Salons A, B, and C of the Gaithersburg Marriott, 9751 Washingtonian Boulevard, Gaithersburg, Maryland, at 8:30 a.m., Dr. Jayne S. Weiss, Chair, presiding.

PRESENT:

JAYNE S. WEISS, MD	Chair
SARA M. THORNTON	Executive Secretary
ARTHUR BRADLEY, PhD	Voting Member
MICHAEL R. GRIMMETT, MD	Voting Member
ALICE Y. MATOBA, MD	Voting Member
TIMOTHY T. McMAHON, OD	Voting Member
ALLEN C. HO, MD	Voting Member
ANNE L. COLEMAN, MD, PhD	Voting Member
TERRI L. YOUNG, MD	Consultant, deputized to vote
GLENDA V. SUCH, MEd	Consumer Representative
RONALD E. McCARLEY	Industry

Representative

FDA PARTICIPANTS:

A. RALPH ROSENTHAL
JAN C. CALLAWAY
JAMES F. SAVIOLA, OD
DONNA R. LOCHNER
BERNARD P. LEPRI, OD, MS, MEd
DON CALOGERO

A-G-E-N-D-A

OPEN SESSION

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

8:30 a.m.

CHAIRPERSON WEISS: I would ask all the panel members to be seated, please. I would like to call this meeting of the Ophthalmic Devices Panel to order and we will have introductory remarks by Sally Thornton.

EXECUTIVE SECRETARY THORNTON: Good morning. Permit me to introduce myself. I am Sara Thornton, otherwise known as Sally, the Executive Secretary of the Ophthalmic Devices Panel. On behalf of the FDA I would like to welcome you to the 105th meeting of the panel.

Before we proceed with today's agenda I have a few short announcements. I would like to remind everyone to sign in on the attendance sheets in the registration area just outside the meeting room. All public handouts for today's meeting are available at that table.

If you have any messages for panel members and FDA participants, information, or special needs, they should be directed through Ms.

Anne Marie Williams, who is sitting by the door there, who is available in the registration area also. The phone number for calls to the meeting area is 301-590-0044.

In consideration of the panel, the sponsor, and the agency we ask that those of you with cell phones and pagers either turn them off or put them on vibration mode while in this room and to make your calls outside the meeting area.

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

Now, at this time I would like to extend a special welcome and introduce to the public the panel and the FDA staff, a new panel consultant who is with us at the table for the first time.

Dr. Terri Young, who is seated to my left, who comes to us from Philadelphia, Pennsylvania, where she is an Associate Professor of Ophthalmology and Pediatrics and Director of the Ophthalmic Genetics Research Laboratory and

Ophthalmic Genetics Clinic at the University of Pennsylvania's Children's Hospital.

Welcome to our table, Terri.

Will the remaining panel members please introduce themselves beginning with Mr. Rick McCarley.

MR. McCARLEY: I'm Rick McCarley, President of Ophtec, and I'm the industry representative.

DR. GRIMMETT: I'm Michael Grimmett, Assistant Professor of Bascom Palmer Eye Institute in Miami, Florida.

DR. McMAHON: I'm Tim McMahon, Professor of Ophthalmology at the University of Illinois in Chicago.

MS. SUCH: I'm Glenda Such, Lighthouse International, New York City.

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

DR. BRADLEY: Arthur Bradley, Professor

of Vision Science, Indiana University.

DR. MATOBA: Alice Matoba. I'm Associate Professor of Ophthalmology, Baylor College of Medicine, Houston, Texas.

DR. HO: Allen Ho, Associate Professor at Wills Eye Hospital.

DR. COLEMAN: Anne Coleman, Associate Professor of Ophthalmology at UCLA in Los Angeles.

DR. ROSENTHAL: Ralph Rosenthal, Division Director, FDA.

EXECUTIVE SECRETARY THORNTON: Now I would like to read the conflict of interest statement.

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

To determine if any conflict existed the agency reviewed the submitted agenda for this meeting and all financial interest reported by the committee participants. The conflict of interest

statutes prohibit special Government employees from participating in matters that could affect their or their employer's financial interest.

However, the agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved, is in the best interest of the Government.

Therefore, a waiver under 18 USC 208(b)(3) has been granted to Dr. Jayne Weiss for her consulting with the competitor's unrelated product. We receives less than $10,001 a year. The waiver allows this individual to participate fully in today's deliberations. Copies of this waiver may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Anne Coleman, Allen Ho, Michael Grimmett, Jayne Weiss, and Terri Young. These

panelists reported current and/or past interest in firms at issue but in matters that are not related to today's agenda. The agency has determined, therefore, that they may participate fully in the panel's deliberations.

We would also like to note for the record that Mr. Ronald McCarley, who is industry representative at this meeting, is the president of a firm at issue. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

I would like now to read the appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices

Advisory Committee charter dated October 27, 1990, and as amended August 18, 1999, I appoint the following individual as a voting member of the Ophthalmic Devices Panel for this meeting on May 23, 2003, Terri L. Young, M.D.

For the record, this individual is a special Government employment and consultant to this panel or other panels under the Medical Devices Advisory Committee. She has undergone the customary conflict of interest review and has reviewed the material to be considered at this meeting. Signed, David W. Feigel, Jr., M.D., M.P.H., Director for the Center for Devices and Radiological Health dated May 13, 2003.

Thank you, Jayne.

CHAIRPERSON WEISS: Thank you, Sally.

The open public hearing portion of this meeting will now begin. Any speaker who wishes to make a presentation before the committee is doing so in response to the panel meeting announcement in the Federal Register. They are not invited to speak by the FDA, nor are their comments, data, or

products endorsed by the agency.

Scheduled speakers are given a 10-minute limit. I will recognize unscheduled speaker as time allows. Those who wish to speak are asked to state for the record their association with the sponsor or sponsors of any product being considered by the panel at this meeting whether you are an investigator or consultant, study subject, etc.

Please state whether you are receiving reimbursement from any device firm for your presentation, transportation, or other expenses to appear at this meeting. Lastly, you will need to state if your organization receives funding from a sponsor whose product is being considered or from a sponsor of a competing product.

I may ask the speaker to remain at the podium if the panel members wish to question them further. Only members of the panel may question speakers during the open public hearing. Is there anyone who is going to be coming to the podium for this?

EXECUTIVE SECRETARY THORNTON: There have

been no scheduled speakers.

CHAIRPERSON WEISS: Seeing no speakers, we will now close the open public hearing and move on to the open committee session beginning with the FDA division update.

DR. ROSENTHAL: I just wanted to make a couple comments. After many years of not being able to hire anybody, we have been given leave to hire people for the division because of the new Medical Device User Fee Act. We will be searching for individuals to come and work for the FDA. If anyone has anyone that might be interested, we'd be delighted to hear from them.

The other thing is Dr. Saviola said he wasn't going to give an update on this issue but I just read in the American Academy of Ophthalmology Washington Report which is a public document that Congress has introduced the Plano Lens Bill.

The bill was introduced by Representative Henry Waxman and Representative John Bosman that amends the Federal Food, Drug, and Cosmetic Act to recognize and regulate both corrective and non-

corrective contact lenses as medical devices regardless of their intended use. Thank you.

CHAIRPERSON WEISS: Thank you very much, Dr. Rosenthal.

Dr. Saviola.

DR. SAVIOLA: Good morning. I intend to update on FDA matters. That's why I deferred to Ralph that last note.

In the Federal Register of April 4, 2003, FDA published a Notice of Availability for guidance to FDA staff on sampling or detention without physical examination of decorative contact lenses.

The document includes FDA's guidance to FDA district offices for sampling or detention without physical exam of Plano zero-powered non-corrective contact lenses that are intended solely to change the appearance of the normal line of decorative fashion when these products are presented for importation to the United States.

Section 201(i) of the Food, Drug, and Cosmetic Act defines cosmetic to include articles intended to be rubbed, poured, sprinkled, or

sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance.

Decorative contact lenses are articles intended to be introduced into the eye which is part of the body to beautify the wearer, promote the attractiveness of the wearer, or alter the wearer's appearance.

Their claim to achieve their cosmetic result by changing the apparent color of the iris by appearing to add a design to the iris. For example, a professional sports team insignia, or by imparting a non-human or otherwise non-normal appearance to the eye like a cat's eye.

Provided they are not marketed with claims that they affect the physical or physiological change to the eye, decorative contact lenses are properly regulated as cosmetics under the act. The courts have read statutory definitions employing the term "intended" to refer to specific marketing representations.

The fact that contact lenses are devices in the colloquial sense does not preclude cosmetic status under the act. FDA has previously determined that Section 201(i) of the Act applies to appearance enhancing devices. Also the fact that a product is intended to come into contact with the eye does not make it ineligible for cosmetic regulation.

On October 22, 2002, FDA issued an import alert with respect to decorative contact lenses. The revised import alert, as noted in the Federal Register, does not cover contact lenses that are intended for vision correction or for prosthetic or other medical use.

There are some lenses currently on the market under 510(k) covering contact lenses intended for both vision correction and decorative purposes. The sponsors in these cases voluntarily included a Plano Lens in the power range of the corrective powers described in the 510(k) submission.

These products are regulated by FDA as

medical devices under the act. Such control is not available for decorative contact lenses because these products are cosmetics under the act.

Section 801(a) of the Act authorizes FDA to refuse admission of articles that appear to be adulterated or misbranded. The guidance represents the agency's current thinking on the sampling or detention without physical exam for decorative lenses that appear to be adulterated or appear to be misbranded. Please read the Federal Register notice for more detailed discussions of adulteration or misbranding of these products.

I have prepared -- out on the table there's a piece of paper, I think it's in your packets, which has all the different websites that are pertinent to that discussion.

I just want to comment that FDA has taken a very strong position that it is necessary to have involvement of an eye care provider to fit and follow soft Plano Lens wearers to better manage risks associated with their use.

This position is described in a press

release that warned consumers about the risk of permanent eye injury and even blindness associated with decorative contact lenses distributed without a prescription and without proper fitting by an eye care professional.

The center also issued a public health web notification directed at health professionals that noted the significant risk of blindness and other eye injuries if non-corrective or cosmetic lenses are distributed without an eye care professional's involvement.

Also an article appeared in the FDA consumer magazine. The press release web notification professionals and consumer articles information on how to report problems to the FDA under the Medwatch program.

The FDA Medwatch database subsequently recorded over 10 reports of decorative or colored contact lens events since the warnings last fall. This may not seem like many but the total for previous years combined was equal in a few month's time. I would like to encourage all eye care

professionals to document cases of contact lens related injuries via the Medwatch program.

Until the update that Dr. Rosenthal gave on the legislation passes, that's the way things are handled right now, that those lenses are going to be regulated as cosmetics. Thank you.

CHAIRPERSON WEISS: Thank you.

Jan Callaway.

MS. CALLAWAY: Good morning. We have had two PMA approved devices since the last panel update of August 2002. On October 28, 2002, we approved P970043, Supplement 10, for the Alcon LADARVision 4000 Custom Cornea indicated for wavefront-guided Lasik for the reduction or elimination of myopia up to seven diopters with less than .5 diopters of astigmatism at the spectacle plane.

On February 25, 2003, we approved P990027, Supplement 4, for the Bausch & Lomb TECHNOLAS 217A Excimer Laser System indicated for lasik treatments for the reduction or elimination of low to moderate naturally occurring hyperopia of

1 to 4 diopters with or without refractive astigmatism up to 2 diopters.

Since August 2002 we have cleared approximately 30 510(k)'s. On January 1, 2003, we lost the services of Gwen Hong, an engineer and team leader in DSDB who transferred to the Office of Surveillance and Biometrics in the Center for Devices and Radiological Health.

In April 2003 we sent a form letter to all IDE sponsors suggesting that even if they had a previous PMA approval they should meet with us prior to submitting their PMA.

This pre-PMA meeting will provide an opportunity to pass along information regarding appropriate endpoints, stability information, safety and effectiveness tables, and formatting for labeling of the PMA with the hopeful result being a more manageable PMA for both FDA and the sponsor with fewer deficiencies identified during FDA review. Thank you.

CHAIRPERSON WEISS: Thank you.

Donna Lochner.

MS. LOCHNER: P010059 is the premarket approval application for Morcher GmbH and capsular tension ring used for capsular bag stabilization in patients with pseudoexfoliation syndrome or other situations of compromised zonulars.

This PMA was reviewed by the Ophthalmic Devices Panel in January of 2002. The panel recommended that the PMA was approvable with request for essentially a complete reanalysis of the clinical data to resolve discrepancies in the PMA and to clarify information presented at the panel meeting.

At this time the PMA has not yet been approved. We are currently working with the sponsor to resolve the remaining issues. Thank you.

CHAIRPERSON WEISS: Thank you for that update. We will now go on to the sponsor presentation. I would like to move to the review of PMA P030002 and invite the first presenter to come to the podium.

The sponsor has one hour. I would like

each presenter to identify themselves and I will remind you to identify any financial interest that you may have at the beginning of the presentation.

MR. KRAMSKY: Good morning. My name is Paul Kramsky. I'm Vice President of Regulatory Affairs and Quality Systems for C&C Vision. We are pleased to present to you today PMA P030002 for the CrystaLens silicone posterior chamber accommodating intraocular lens for implantation of patients with cataracts.

Presenting on behalf of C&C Vision today will be Dr. Michael Breen from our clinical staff, and Dr. Stephen Slade, Michael Colvard, and Adrian Glasser, all of whom are consultants and have a financial interest in C&C Vision. Dr. Judy Gordon, a clinical regulatory consultant for C&C Vision will facilitate discussions.

The CrystaLens has the same indications for use as any standard intraocular lens that is intended for primary implantation for the visual correction of aphakia in adult patients with cataracts.

Additionally, the CrystaLens provides patients with improved vision at near, intermediate, and distance without spectacles as will be established in our presentation of the clinical trial conducted in support of this PMA.

The first presentation this morning will be made by Dr. Michael Breen, Director of Clinical Outcomes for C&C Vision.

DR. BREEN: Good morning. My name is Dr. Michael Breen and I will review the developmental history of the CrystaLens, the product specifications, and the proposed mechanism of action.

Since this is the first accommodating IOL to be reviewed by this panel, we would like to start with the definition of accommodation. While a review of the published literature on this subject provides a number of definitions and descriptions of accommodation, we believe the best description defines what is ultimately important to the

patient - the ability of the eye to change focus

and to afford the patient a clear image over a range of distances.

Generally, monofocal IOLs have been used to provide the postoperative cataract patient with functional distance vision. Patients usually require a correction for intermediate and near vision. Consequently, there has been a great deal of interest in finding treatment modalities that can provide postoperative cataract patients with intermediate and near vision in addition to distance vision.

A number of options for providing near vision in pseudophake patients has been evaluated with varying degrees of success including monovision, implantation of multifocal and bifocal intraocular lenses which are available commercially, and now an accommodating intraocular lens which is the subject of our presentation.

The premise for the development of an intraocular lens that can accommodate as suggested by a body of published literature, Fisher established that the ciliary muscle maintains

functional activity with age. This was confirmed by Strenk and Colleagues using magnetic resonance imaging, or MRI, to show that the ciliary muscle retains much of its contractility in older patients.

In clinical practice Cumming showed that plate lenses fall against the vitreous face and further observed that in some patients implanted with plate lenses the optic may move forward following pilocarpine administration.

Coleman's observations in primate eyes that electrical stimulation of the ciliary muscle results in accommodation with an accompanying increase in vitreous cavity pressure and a simultaneous decrease in anterior chamber pressure suggest the basis for the experience of Cumming and other surgeons using plate lenses.

Taken together, these findings suggest that an appropriately designed intraocular lens might have the ability to move along the axis of the eye as a result of pressure changes between the anterior chamber and the vitreous cavity leading to

the development of the CrystaLens.

The CrystaLens is a modified plate haptic lens with a biconvex optic. The optic material was a third generation silicone with a refractive index of 1.43 and a UV filter. The plate length is 10.5 millimeters. The overall length of the lens measures 11.5 millimeters and the optic diameter is 4.5 millimeters.

The lens has hinges adjacent to the optic allowing forward and backward movement of the lens along the axis of the eye. The polyamide loop provides fixation, centration, and stability of the lens in the capsular bag.

This slide summarizes the proposed mechanism of action of the CrystaLens. As previously mentioned, studies by Busaka and Strenk, et al., suggest that the ciliary muscle contraction in relaxation results in the redistribution of muscle mass.

Further, Strenk, et al., showed that active ciliary muscle contraction still occurs with an accommodative effort in subjects up to 83 years

old. In 1986 Coleman showed a differential pressure increase in the vitreous cavity with accommodation in primates.

The CrystaLens is designed to take advantage of vitreous cavity pressure changes by locating against the vitreous face. This allows the lens optic to move forward and backward in response to ciliary muscle contraction and relaxation and altering pressure changes between the vitreous cavity and the anterior chamber. The hinged haptics facilitate axial movement of the CrystaLens by minimizing resistance.

This image of an eye implanted with the CrystaLens one day after surgery was captured with Scheimpflug technology. This shows the desired posterior position against the vitreous.

Development of the CrystaLens was conducted according to FDA guidance in ISO standards protesting of intraocular lenses with additional testing performed to address the specific characteristics of the lens. This testing included biocompatibility, effective YAG laser in

vitro, hydrolytic stability, photostability, and exhausted extraction.

Optical and mechanical testing was also performed and included dynamic fatigue testing to establish the durability of the hinge. All testing was successfully completed and was submitted to the FDA initially as part of the IDE application and also as part of this PMA.

Now it is my pleasure to introduce Dr. Stephen Slade who will present the study design and the visual acuity outcomes.

DR. SLADE: Thank you, Michael. Good morning. I'm Steve Slade, investigator and medical monitor for the C&C Vision CrystaLens Accommodating IOL Study. I do have a financial interest in C&C Vision.

It's my pleasure to present to you the study design and visual acuity results from this perspective multi-center clinical investigation. We had 14 U.S. clinical investigators and three non-US sites contributing to this clinical trial.

The clinical trial for the CrystaLens was

conducted under an FDA approved IDE and was designed according to FDA guidance for intraocular lenses and draft guidance for multifocal intraocular lenses. Subjects were required to be at least 50 years of age with cataracts.

Potential for best corrected visual acuity of 20/32 or better was required. Eyes with more than a diopter of corneal astigmatism were excluded from participation. Follow-up exams were conducted at traditionally accepted intervals over the course of our one-year study.

Multiple measures of near, intermediate, and distance visual acuity were performed on the entire study population. However, as defined in the IDE study protocol, the primary measure of accommodative functionality of the CrystaLens was near vision measured through the patient's distance correction obtained by manifest refraction.

By measuring near vision through the patient's distance correction, we eliminated residual myopia and astigmatism which can contribute to functional near vision. Uncorrected

near vision was measured as well. Intermediate visual acuity was measured both through the distance correction and without correction for our bilaterally implanted subjects.

Finally, both uncorrected and best corrected distance visual acuity were measured for all study eyes. Monocular visual acuities will be shown for the primary eyes, first implanted in each subject, and monocular visual acuities are shown for our subject bilaterally implanted subjects. Unless otherwise indicated, visual acuities are presented for the one-year follow-up.

Standardized methods and equipment were used for all measurements of visual acuity at all U.S. clinical sites with rigorous control of lighting and chart distances. Distance visual acuity was measured using the Stereo Optical Optec X1600 equipped with an ETDRS acuity chart and luminance of 85 cd/m2.

These units were calibrated for a 20-foot or six meter testing distance. Near an intermediate acuity were measured using MNREAD

acuity chart shown here also using a luminance of 85 cd/m2.

This is a logMAR chart with text rather than individual optotypes and is, therefore, considered a test of functional vision. Near visual acuity was tested at 16 inches or 40 centimeters. Intermediate visual acuity was tested at 32 inches or 80 centimeters.

Testing distances were kept constant from site to site, patient to patient, by fitting the charts with a nylon cord that was marked at 16 and 32 inches.

Testing distances were verified prior to each intermediate and near visual acuity measurement. The lighting in each exam room at every site was calibrated frequently during the course of the study to ensure the luminance required remained constant for all patient examinations.

A total of 497 eyes of 324 subjects were implanted with the CrystaLens at the 17 clinical sites. Consistent with other trials of intraocular

lenses there were more females enrolled than males and the mean age of the study patients was 69.7 years.

The study cohort of 497 eyes represents 324 primary eyes and 173 fellow eyes. Per FDA guidance for clinical trials of intraocular lenses, analysis of safety and effectiveness are based on the primary eyes rather than the total eyes implanted, although complete data on all implanted eyes were provided in our PMA submission. During our presentation visual acuity measured binocularly will be shown for the bilaterally implanted subjects.

The safety cohort consisted of all 324 eyes while the effectiveness cohort consisted of 263 eyes implanted and followed at the U.S. clinical sites. Eyes implanted at the non-U.S. sites are not included in the effectiveness cohort since nonstandardized charts were used as MNREAD charts are not available in languages required, specifically French and Portuguese. Accountability for the effectiveness and safety cohorts at one

year was over 93 percent.

I'll be presenting outcomes for measurement of near, intermediate, and distance visual acuity follow-up. As I have already mentioned, monocular visual acuities are shown for the primary eyes, first eye implanted in each subject. Monocular visual acuities are shown for our subset of bilaterally implanted subjects.

This is the MNREAD chart which I have shown you. Here we have outlined the 20/40 line. We all talk about visual charts. We all spend considerable time in sharing standardization. For this presentation, though, we wanted to go a step further and try to highlight what our results really mean to patients in day-to-day settings.

20/40 line corresponding to 6 point font is shown here. The MNREAD charts, again, require patients to read text as a measure of functional vision in contrast to charts that show single optotypes.

Keeping the same 20/40 text centrally on the screen, we would like to show you an important

example of a real life near vision reading situation, an Advil bottle with 20/40, or 6 point font.

As we go through the visual acuity data results for the study population, we hope this will help illustrate the accommodated benefits provided by the CrystaLens, especially considering 93.8 percent of our bilaterally implanted subjects had uncorrected near visual acuity of 20/32 or better at one year.

Now, uncorrected near visual acuity is displayed on this slide for the total cohort of 241 primary eyes. Binocular uncorrected visual acuity was available at one year for 124 of our 127 bilaterally implanted subjects.

88.4 percent of primary eyes and 98.4 percent of the bilaterally implanted subjects achieved uncorrected near visual acuity of 20/40 of better. 93.5 percent of the bilaterally implanted subjects achieved 20/32 or better, near visual acuity through the distance correction.

Near vision was also measured through the

subject's distance correction obtained by manifest refraction. By measuring near vision through the distance correction we eliminated residual myopia and astigmatism which can contribute to functional near vision.

90.1 percent of the primary eyes achieved distance corrected near visual acuity of 20/40 or better while 100 percent of the subjects implanted bilaterally achieved distance corrected near visual acuity of 20/40 or better.

Now, while accommodated functionality in the study population is established by measuring near and intermediate visual acuity through the distance correction to eliminate myopia and astigmatism as confounders, what the patient really wants is a full range of vision without spectacles including uncorrected near vision.

This slide shows monocular near acuity for eyes with postoperative refractions within a half a diopter of plano set for distance to eliminate those eyes with postoperative refractive errors of myopia and hyperopia. This represents

163 of our primary eyes, 243. 89.6 percent of these eyes with good distance refractive outcomes achieved uncorrected near acuity of 20/40 or better which corresponds to J3 on the familiar Jager chart.

Intermediate visual acuity measured through the distance correction for primary eyes and for bilateral implants subjects also is excellent. 95 percent of our primary eyes and 100 percent of the bilateral implants subjects achieved an intermediate visual acuity of 20/25 or better through their distance correction. Additionally, 98.4 percent of the bilateral implanted subjects achieved an uncorrected intermediate acuity of 20/25 of better.

The results for uncorrected distance visual acuity for primary eyes and bilateral implanted subjects at one year are combined on this slide. 88.9 percent of the primary eyes corrected distance visual acuity of 20/40 or better.

The percentage of bilaterally implanted eyes in blue achieving uncorrected distance visual

acuity of 20/25 or better was 91.9 percent with 97.6 percent achieving 20/32 or better and 98.4 achieving 20/40 or better.

Uncorrected distance acuity for eyes with a good refractive outcome postoperatively within half a diopter was also excellent with 97 percent of eyes with this refractory outcome achieving an uncorrected distance acuity of 20/40 or better and 86.7 percent of these eyes at 20/25 or better.

The safety of this lens was also very good with 96.7 percent of primary eyes and 100 percent of bilateral implanted subjects correctable postoperatively to 20/25 or better. A key measure of the function of an accommodating intraocular lens is whether the same eye or the same subject achieved both near and distance visual acuity, uncorrected and distance corrected.

78.8 percent of our primary eyes had both uncorrected near and distance visual acuity of 20/40 or better. While in our bilaterally implanted subjects, 96.7 percent achieved uncorrected visual acuity of 20/40 or better at

both distance and near.

To further substantiate functionality of an accommodating IOL the confounding myopia and astigmatism should be eliminated by measuring acuity to the distance correction. 89.6 percent of our primary eyes and 100 percent of our bilaterally implanted subjects had both near and distance acuity of 20/40 or better through their distance correct.

We would like to present further key study findings including the effective biometry method on the visual acuity, the effect of the subject age on the near visual acuity, effective YAG capsulotomy on near acuity, the stability of the near visual acuity over time, and the stability of the manifest refraction over time.

To evaluate the effect of biometry, we compared uncorrected near visual acuity from non-immersion versus immersion methods. While biometry had only a limited impact on uncorrected near acuity at the 20/40 level, a significantly larger portion of eyes achieved uncorrected near acuity of

20/32 or better when immersion biometry was used.

Similarly, use of immersion biometry resulted in a larger proportion of eyes with uncorrected distance acuity of 20/32 or better. But the outcomes were generally good regardless of the method used.

Did younger subjects have better outcomes than older subjects? When we stratified our cohort by age and decades there were no statistically significant differences in outcomes suggesting an equally good accommodated functionality even in the older study subjects.

Could capsular fibrosis interfere with lens functionality? In fact, distance corrected near acuity was generally unchanged from the early postoperative period through 11 to 15 months in blue. These data address concerns that the natural course of capsular fibrosis may reduce the accommodative ability of the lens over time.

The stability of near visual acuity through the distance correction is further confirmed by looking at changes in lines of vision

over time. Overall 79 percent -- 79.8 percent of the eyes remained within one line across the study visits shown.

Did a YAG capsulotomy affect the functionality of the lens? We compared near vision through the distance correction for eyes that had YAG capsulotomy to non-YAG with documented clear posterior capsules. Eyes with any trace of posterior capsular haze were excluded from the non-YAG group.

There was no difference in distance corrected near visual acuity for eyes that had undergone YAG laser capsulotomy as compared to the non-YAG population of eyes. It should be noted there were no specific criteria in the study for performing YAG capsulotomy and the pre-YAG best corrected distance visual acuity was 20/25 or better and 30 of the 34 YAG eyes. Draft labeling for the CrystaLens recommends limiting the size of the YAG capsulotomy to no more than 4 millimeters.

Another question was raised in regard to stability of the hinge. To address this we looked

for change in manifest refractive spherical equivalence stability over time in a consistent cohort of primary eyes. In fact, refractive stability was very good. 85 percent of eyes changing by a half a diopter or less and 96.6 percent of eyes changing by a diopter or less over the study follow-up.

A patient survey was administered to all study subjects at the one year examination. Now, since several subjects mailed their surveys before the one year examination, we are reporting on the total of 130 subjects. Not all survey items were applicable to every subject. Thus, there is a different total number of subjects for each survey item.

93.8 percent of bilaterally implanted subjects were able to perform most daily activities without spectacles. This is in an average age of 69 years. We learned, too, that we had a fairly visual demanding cohort with a large proportion of these subjects actively working on the computer, driving, etc.

When specifically asked, "How often do you wear spectacles," the majority of our bilaterally implanted subjects responded, "Almost none of the time." Only 11 percent of subjects indicated any significant spectacle use at all.

Overall quality of vision was rated as very good to excellent by 82.5 percent of the bilaterally implanted subjects. In fact, only four subjects reported poor near vision with none reporting poor intermediate vision or poor overall vision. None of those four subjects had worse vision than 20/40 at any distance.

Now, I would like to close this section of our presentation by illustrating the functional vision that a patient can achieve by having at least 20/40 uncorrected near vision. Some of our favorite literature, indeed, is easier than 20/40 such as the blue journal at 20/50 8 point font.

Looking at 20/40, therefore, or better visual acuity in our cohort, the accommodative functionality of the CrystaLens was clearly established with measurement of near and

intermediate acuity through the distance correction to eliminate the confounders of myopia and astigmatism.

Distance corrected near visual acuity of 20/40 or better was achieved by 90.1 percent of the primary eyes and 100 percent of the bilateral subjects. To further illustrate the range of vision, intermediate visual acuity distance corrected was achieved by 99.6 percent of the primary eyes and 100 percent of all the bilateral subjects. That represents all but a single primary eye.

More importantly, 89.6 percent of the primary eyes and 100 percent of the bilaterally implanted subjects achieved both near and distance visual acuity of 20/40 or better through their distance correction. Again, this metric establishes the functionality for an accommodating IOL by eliminating myopia and astigmatism.

Finally, for a patient's perspective we looked at our bilaterally implanted subjects over the range of acuities measured without glasses in a

real life setting. Again, please keep in mind that the mean age of this population was over 69 years.

Given that fact, 93.5 percent read 20/32 or better at near, 100 percent had an uncorrected intermediate vision of 20/32 or better, and 97.6 percent achieved uncorrected distance acuity of 20/32 or better.

It's now my pleasure to introduce Dr. Michael Colvard.

DR. COLVARD: Thank you, Steve. Good morning. I'm Mike Colvard and I served as a study investigator and I have financial interest in C&C Vision.

I'll be presenting the results of the substudy conducted by C&C Vision to evaluate the performance of the CrystaLens under low light or mesopic conditions. This substudy was undertaken to address concerns related to the 4.5 millimeter optic by comparing contrast sensitivity in eyes implanted with CrystaLens with a matched group of subjects implanted with standard intraocular lens.

The subgroup of total CrystaLens population and a matched cohort of eyes were implanted with the standard IOL constituting the study population.

Control group of implanted eyes with standard IOL met the same eligibility criteria as the CrystaLens population and underwent surgery during the same period of time. Contrast sensitivity was measured at three to six months postoperatively or later and if posterior capsular classification was present, the testing was delayed until after the YAG capsulotomy had been performed.

Equipment used was the Stereo Optical Optic 1600 vision tester. Testing was performed with mesopic lighting of 3 cd/m2. Patients were allowed to dark adapt for 10 minutes after which the mesopic testing was performed with and without a glare source of 3 lux. Units were calibrated for measurement at 20 feet.

A ratio of two to one of CrystaLens versus standard IOL was selected. The sample size of 125 CrystaLens implanted eyes and 64 control

eyes was determined. This provides an 80 percent power to establish the contrast sensitivity for the CrystaLens group is not worse than the standard IOL group with a significance of .05, an acceptable difference between the two groups of .12 log units.

In this test patients were asked to review a series of eight patches at each of five spatial frequencies ranging from 1.5 cycles per degree to 18 at decreasing levels of contrast. As shown on this slide, there were no differences between the CrystaLens and the standard IOL groups at any spatial frequency when testing was performed with mesopic luminance without glare. The addition of a glare source showed no difference between these two study groups.

In summary, there was no difference in contrast sensitivity between the CrystaLens and the standard IOLs. Importantly, glare had no effect on contrast sensitivity outcomes in the CrystaLens implanted eyes.

I would now like to present the safety results for the CrystaLens clinical trial.

Cumulative adverse events are those which occur at anytime over the course of the study in contrast to persistent adverse events which are present at the time of one year visit.

In this slide the cumulative adverse events were all primary eyes. You can see that there was one case of endophthalmitis and one case of hyphema both of which were reported from non-U.S. sites, two secondary surgical interventions and 12 cases of CME. All these were diagnosed by fluorescent angiography.

Two secondary surgical interventions consisted of a vitrectomy and a lens repositioning. The incidence of CME higher in the study group than the FDA grid 3.7 versus 3 percent.

Cumulative adverse events for all 497 implanted eyes are shown here. There was one additional case of CME in one fellow eye and four additional secondary surgical interventions. The secondary surgical interventions consisted of one lens repositioning when a small tear was noted postoperatively in the anterior capsule, two

explanations, and a paracentesis.

The paracentesis was performed to reduce intraocular pressure on the first postoperative day. One explanation was the result of an incorrect power selection. The other explanation resulted from an excessively large capsulorhexis that allowed anterior vaulting of the lens.

As shown on this slide, of the 13 eyes diagnosed with CME, only five of the eyes have visual acuity of 20/40 or worse at the time of diagnosis. At the last available visit best corrected visual acuity was 20/40 or better for all eyes with the exception of a single eye with posterior capsular classification.

In summary, seven of the 13 eyes had best corrected visual acuity of 20/25 or better at the last available visit, 10 eyes of 20/32 or better and all eyes with the exception of a single eye with posterior capsular classification with 20/40 or better.

Persistent adverse events are events present at the one-year follow-up. As shown on

this slide, four persistent adverse events were reported of three primary eyes implanted with a CrystaLens, one eye presented with both CME and iritis at one year.

This eye had residual cortex in the anterior chamber at the end of surgery that was still present at the one-year visit. The second eye had persistent iritis at one year. A third eye in this group had persistent CME at one year. Overall, the percentage of eyes with iritis and with CME was slightly higher than the FDA grid values.

This slide shows persistent adverse events in all 450 implanted eyes. You can see that there was one additional case of iritis and one additional case of CME each reported in one patient.

Persistent adverse events for the total study population of 450 implanted eyes is shown here. Iritis and CME were reported together in one eye of a single patient. At the last follow-up all eyes had best corrected visual acuity of 20/32 or

better.

In conclusion, the CrystaLens has a solid safety profile. The incidence of iritis and CME are higher in the safety cohort of primary eyes than the FDA grid of historical controls. However, at one year all the study eyes with CME or iritis had best corrected visual acuity of 20/32 or better. No serious or unanticipated adverse events related to the CrystaLens were reported at anytime during the course of the study.

I would now like to introduce Dr. Adrian Glasser, University of Houston, to discuss results of testing for accommodation with the CrystaLens.

DR. GLASSER: Thank you, Michael. Ladies and gentlemen of the panel and the Food and Drug Administration, my name is Adrian Glasser. I am a consultant for C&C Vision and I have a financial interest in the company.

There has been a long-standing debate as to what the mechanism of accommodation is, how it should be assessed, and the mechanism by which it occurs. A quote that I often use from Helmholtz's

Treatise on Physiological Optics emphasizes the long-standing debate that continues today.

Helmholtz wrote, "There is no other portion of physiological optics where one finds so many differing and contradictory ideas as concerns accommodation of the eye. Where only recently in the most recent time have we actually made observations where previously everything was left to the play of hypotheses."

Almost 80 years later Michaels wrote, "Accommodation is one of those subjects about which much that is supposed to be known has yet to be discovered. The anatomy is controversial, the mechanics theoretical, the innovation doubtful, the stimulus debated, the resting state in flux, the pharmacology uncertain," etc. Much of this uncertainty still exist today.

This slide shows several authoritative definitions of accommodation. The two dictionary definitions identify a causal role in accommodation from changes in the crystalline lens surface curvatures.

These two statements were made about the physiological accommodation with the natural crystalline lens in the eye. It has been difficult to define accommodation and to ascertain the accommodative mechanism in the phakic eye. It is equally difficult to define and characterize the mechanism of pseudo phakic accommodation.

More clinically accepted, although no more or less accurate definitions of accommodation, include that from Tscherning and Griffin. The C&C Vision CrystaLens does not undergo a change in lens surface curvature. So from a clinical perspective the working definition of accommodation considers the range of clear vision that patients experience or the dioptric distance between the near point and the far point.

The C&C Vision CrystaLens was designed to capitalize on forward movement of the optic that was observed to occur with an accommodated effort in pseudophakes with plate lenses.

As shown before, the proposed mechanism of action of the C&C Vision CrystaLens is to move

the optic forward in the eye with the contraction of the ciliary muscle through an increase in vitreous cavity pressure.

In 1999 when this IDE was first presented to the FDA and the clinical trial initiated, pseudophakic accommodation was a relatively new concept. Although there is now considerably more interest in pseudophakic accommodation, there are still no studies that have validated clinical methods to measure pseudophakic accommodation.

While clinical refractometers work well in normal phakic eyes, the testing is often difficult and inconsistent in pseudophakes. Just as accommodative lens technology is in its infancy, so too is the technology for reliable pseudophakic accommodation measurement.

Clinically postoperative refractive outcomes in cataract patients are most often assist quite simply with best corrected distance acuity behind the foropter.

Having said that, in the CrystaLens clinical trial 10 eyes of five subjects underwent

more extensive accommodation testing by one of the clinical investigators. This testing was done using tests that the investigator was familiar with and uses clinically to assess accommodation.

There is no question that some of the methods used are not objective tests. The tests included dynamic retinoscopy and defocus with minus lenses. In addition, a Tracey wave tracing wavefront aberrometer was used.

Accommodative movement of the IOL was also assessed with A-scan optosenography. On one occasion when accommodation was first paralyzed with 1 percent cyclopentolate and then again at a later time when accommodation was stimulated with 6 percent pilocarpine.

The A-scan data show a consistent decrease in anterior chamber depth and the forward movement of the CrystaLens. If an IOL moves forward in the eye, this would cause an accommodative change in power with the eye, i.e., pseudophakic accommodation.

Although the testing was done in only a

limited number of eyes with both subjective and objective tests, the study results show with one exception consistent changes that are representative of accommodative change.

The sponsor acknowledges Dr. Bradley's valid concerns about the limitations of the accommodation testing performed. But the measured change in anterior chamber depth shown here show a forward movement of the CrystaLens in nine out of 10 eyes.

The sponsor agrees that these data by themselves do not prove the mechanism of accommodation. Having said that, the lens was designed to move forward with an accommodative effort and the limited data shown here suggest that this is occurring.

This study determined the best distance corrected intermediate and near visual acuity and the add power required to achieve the best possible near vision. In the contrast sensitivity substudy already described, CrystaLens subjects were compared to a group of subjects implanted with a

standard IOL.

As described earlier by Dr. Slade, all patients implanted bilaterally and nearly all with an implant in only one eye achieved excellent near vision through the distant correction with 90 percent of the primary eyes and 100 percent of the bilaterally implanted subjects achieving 20/40 or better. Again, this shows the near visual acuity measured with the confounding factors of myopia and astigmatism removed.

Excellent results were found for the intermediate visual acuity measured through the distance correction as presented earlier by Dr. Slade. All but a single primary eye achieved intermediate visual acuity through the distance correction of 20/32 or better at one year.

The add required to achieve best near visual acuity was evaluated in the CrystaLens and standard IOL subjects in the substudy. Where the CrystaLens subject had a mean measured add of 1.24 diopters, the standard IOL group required a mean measured add of 2.36 diopters.

The graph shows a clear distinction between the CrystaLens subjects and the standard IOL subjects with regard to the add required to achieve best near acuity. The data suggest that the CrystaLens is providing far better functional near vision than the standard IOL and asserts to establish the functional accommodation provided by the CrystaLens.

Here the distance corrected near visual acuity of the CrystaLens subjects were compared to those of the standard IOL subjects. While 35.9 percent of the standard IOL subjects achieved distance corrected near visual acuities of 20/40 or better, 89.3 percent of the CrystaLens subjects achieved this.

Testing was performed during the same postoperative period and the same inclusion criteria were used for the two groups. The testing conditions were identical for the two groups. The difference between the two groups is the IOL. The CrystaLens was designed to capitalize on the observed tendency of plate lenses to undergo a

forward movement with an accommodative effort.

Clinical testing shows that significantly more CrystaLens patients have functional distance corrected intermediate and near visual acuities than patients with standard IOLs. It may be unclear how much of the benefit of the CrystaLens is due to active dynamic accommodation, depth of focus, or ocular aberrations. However, what is clear is that the CrystaLens appears to perform in accordance with the principles for which it was designed.

In summary, despite years of study the mechanism of physiological accommodation is still not fully understood. Pseudophakic accommodation is a new concept and its mechanism is also not fully understood.

The objective measurements of changes in anterior chamber depth show forward movement of the CrystaLens. The near and intermediate visual acuities measured through the distance correction provide evidence of accommodation consistent with the proposed mechanism and the objective

measurement.

This is further established by the fact that the CrystaLens subject required 1.12 diopters less add to achieve best corrected near acuity than subjects implanted with a standard intraocular lens.

Dr. Slade will now summarize and conclude our presentation.

DR. SLADE: Thank you, Adrian. In summary, accommodative functionality of the CrystaLens was clearly established in this clinical trial with measurement of near and intermediate visual acuity through the distance correction to eliminate the confounders of myopia and astigmatism.

Distance corrected, near visual acuity of 20/40 or better was achieved by 90.1 percent of the primary eyes and 100 percent of the bilaterally implanted subjects. Intermediate acuity through the distance correction of 20/40 or better was achieved all but a single primary eye.

Further, 89.6 percent of the primary eyes

and 100 percent of the bilaterally implanted subjects achieved both near and distance visual acuity of 20/40 or better through their distance correction. 93.5 percent read 20/30 or better at near. 100 percent had an uncorrected intermediate vision of 20/32 or better. And 97.6 percent had an uncorrected distance acuity of 20/32 or better.

To conclude, the CrystaLens was designed to provide patients with a full range of clear vision without glasses from near through intermediate and far vision. The results of this PMA clinical trial demonstrate that this goal has been exceeded with over 98 percent of the bilaterally implanted subjects achieving the full range of near, intermediate, and distance vision without glasses.

Thank you very much for your attention and this concludes the sponsor's presentation. Thank you.

CHAIRPERSON WEISS: Thank you, Dr. Slade. I would ask the sponsor if they could all take seats at the table, we'll be going into the 30-

minute question period from the panel.

I have one question in terms of the definition that you gave by Griffin for accommodation, the ability of the eye to afford clear imagery of a stimulus object over a range of distances. Wouldn't a multifocal eye well then be classified as an accommodative eye well through that definition?

DR. GLASSER: This is Adrian Glasser. Technically, yes, with one distinction. The multifocal IOL achieves that result through a very different cause than a monofocal IOL. The CrystaLens is not designed to have multifocality to it so the required action of the lens is the reason that the near, intermediate, and distance visual acuity is being achieved.

But certainly multifocal intraocular lenses were designed for that very reason, to provide functional near and distance vision. One additional feature that an accommodative intraocular lens would provide would be the full range of clear vision, not just near and distance

vision that a multifocal lens may provide.

CHAIRPERSON WEISS: Just a second question and then we'll go on to Dr. Matoba.

You have both near and distance visual acuity for eyes that were in the plus and minus half diopter of Plano. I noted that you did not have that for intermediate visual acuity. Was that done for intermediate visual acuity as well?

DR. BREEN: I'm Michael Breen. I'll repeat my name again. My name is Michael Breen. Those were unilateral uncorrected visual acuities. We did not take or did not measure unilateral uncorrected visual acuity for intermediate vision. That's why it wasn't presented.

CHAIRPERSON WEISS: Thank you.

Dr. Matoba.

DR. MATOBA: This is Alice Matoba. In the protocol I did not see a detailed description of how the manifest refraction was carried out. I wondered if you had given a certain standard protocol for the MR because there is a subjective component both for the patient and for the

refractor.

If you slightly under-correct a myop, then you'll have uncorrected visual acuity at a distance of 24 or better and better near vision as well. Was it mast or was there some standardization for the manifest refractions?

DR. BREEN: This is Michael Breen. I think great pains were taken to make sure that standard procedures were followed with the manifest refraction. The one thing that we did at the three exam which is at one month was to perform a cycloplegic exam which really gave a definitive idea of what the patient's refraction was.

There was a specific refractive procedure followed for every refraction to take great pains not to over-minus the patient but also not to over-plus the patient so that we wouldn't get inaccurate visual acuity measurements when we were measuring the distance corrected intermediate vision and the distance corrected near visual acuity.

DR. MATOBA: Were the refractions masted?

DR. BREEN: No. The refractions were not

masted.

CHAIRPERSON WEISS: Dr. Grimmett.

DR. GRIMMETT: Hi. Michael Grimmett. I have a couple of questions, couple of housekeeping ones. The first one in the criteria it list don't implant the lens if the capsule or axis size is too large. Indeed, one lens was explanted for that reason.

I assume that was judged or measured intraoperatively. Was there a methodology? How exactly did the surgeon know just as a matter of course when he tears a capsule or axis, how large did he know it was?

DR. SLADE: Stephen Slade. We aim to have a capsulotomy around 5 millimeters. The surgeons use different ways to judge that, either a metric or a rule or calipers. But the one patient that did have an explant actually was an oval capsulotomy and the lens was implanted along the long axis of that capsulotomy and did bulk forward. That did not occur except in that one oval capsulotomy case.

DR. GRIMMETT: So they were using some calibers over the cornea to have an estimate.

DR. SLADE: Right. Different surgeons use different techniques.

DR. GRIMMETT: All right. The second question. In Vol. 2 of your manual, I think in Appendix 2, was I think all the protocol forms that you used and all the questions that were answered collecting the data during the study.

There was one particular question that I would be interested in the answer if it exist. Maybe I just didn't spot it in the materials. Page 264 of Vol. 2 had a question at the top that list, "Most people experience some visual disturbances such as glare or halos from looking at oncoming headlights and driving at night."

Since your surgery have these disturbances (a) increased, (b) decreased, or (c) not changed? While I did find tables for night driving activity like Table 10.7, I didn't really exactly see that question answered. Do you have the data for that?

DR. GORDON: I'm going to have to look it up.

DR. GRIMMETT: Okay. I would appreciate it. Thank you.

My third question. In Vol. 1 -- sorry about the tabs here -- Vol. 1, Tab 13 under the summary, page 184. I'll let you turn to that. Do you have it? Okay.

At the bottom where there is a figure 13.2 that list the rate of visual disturbances, specifically glare, halos, and nighttime driving vision for the CrystaLens shown in the white boxes versus a standard IOL which was pulled out of a study by Rogers, Steiner in Ophthalmology in 1999.

It was rather counterintuitive to me that a lens with a smaller optic would have a lower rate of glare, halos, and night driving vision difficulty than a lens with a larger optic. I'm sorry I didn't pull Rogers, Steiner's study but what was the standard IOL that he was using? Do you know was that an AMO standard lens?

DR. SLADE: Steve Slade. I think I can partially address that. I believe that was Rogers AMO study with a 6 millimeter optic. Of course, when you are comparing two surveys from two disparate studies, we found it significant really that we weren't worse and grateful that we were better.

A lot of that has to do with centration because of the length of the haptic lens from a surgeon's viewpoint centers beautifully. It also has nothing intruding within the optic. A staked haptic IOL does have the optics intruding within that 5.5 or 5.6 millimeter optic where this has nothing.

Primarily I believe it was due just to the centration. It centers better than any lens that I've had experience with.

DR. GRIMMETT: And then my final question at this time. There was some issues raised regarding the fatigue factor, the hinge, with one million cycles being tested. I just want a clarification. All these calculations about one

million cycle failure.

Your test did not show that it failed at one million. In fact, it showed that there was no visual fatigue at one million and the actual fatigue time is unknown. It's greater than a million somewhere. Correct?

DR. SLADE: We got tired of watching it flex. That is true.

DR. GRIMMETT: So all these calculations that are basing off one million, that was a time point that it did not show fatigue.

DR. SLADE: We did not see any failures. No, sir.

DR. GRIMMETT: Thank you.

CHAIRPERSON WEISS: Dr. Young.

DR. YOUNG: I'm Dr. Young. It's interesting that the subjects who underwent YAG posterior capsulotomy retained good, near, and intermediate visual acuity and presented a common functionality.

One would expect that this functionality might be compromised once the posterior capsule is

disrupted as it can no longer transmit increased posterior vitreous pressure forces forward to effect an IOL shift anterially. This is especially interesting in this older aged population with increased likelihood of vitreous syneresis and liquefaction.

I did note that in your presentation that you now are recommending a limitation of the capsulotomy size to 4 millimeters or less. The mechanism still as a puzzle may provide some variability with YAG capsulotomy. Can you comment on that?

DR. SLADE: Right. Steven Slade. I'll be glad to comment about that. the patients that had YAG capsulotomy did not show a decrease in their functionality. The CrystaLens is not a bag issue. It does fixate in the bag. The atropine allows it a chance for the specific little polyamide loops to be fibrosed down and captured. But it is really increased pressure, not the vitreous.

These patients obviously had posterior

vitreous detachments in a lot of cases. It's not that. It's the vitreous cavity, pressure within the vitreous cavity which really would not make a difference then whether there is a capsule or just the lens itself. It's pushing against the lens whether it's had a YAG or not.

The capsulotomy on the YAG was kept, we recommend, at 4 millimeters or less because we don't want vitreous coming around. Just one additional point, back to the glare with Dr. Grimmett's comments. This lens is posteriorly positioned dramatically more, as you saw in the photograph, than a standard IOL.

If you figure out on a schematic eye the farther back you push it, the larger the image would be projected then upon the cornea so it actually functions at a larger -- we calculated 5.4 -- than typical. That also might speak to the relatively low incidence of glare. Did that answer your question?

DR. YOUNG: Yes. In your second limited study of 10 patients, did any of those patients

undergo a YAG capsulotomy?

DR. SLADE: That was a subset from another investigator that was not myself but Dr. Dell. I don't know if any of Dell's 10 subset underwent a YAG.

DR. BREEN: I'm Michael Breen. Yeah, we would have to look that up to make sure on that.

CHAIRPERSON WEISS: Dr. McMahon.

DR. McMAHON: Tim McMahon. Continuing along the same lines as Dr. Young, in your draft labeling you discuss the posterior capsular disruption that is indicated not to implant the lens.

Is that what you intend or is it that there will be a limitation in your near visual acuity potential from that? I want some clarification that if you have a tear in the capsule and a need, for example, for an anterior vitrectory, are you going to advise surgeons not to implant this lens?

DR. SLADE: Stephen Slade. I can address that. We do mean that. If there is a tear in the

posterior capsulotomy and an anterior vitrectory, we would suggest that it is not implanted. This lens to function requires to be within the capsular bag. It's a bag lens.

It also being longer is tensioning the capsular bag. In any patient personally with any sort of capsular tear of vitrectory I wouldn't use a capsular in anything that would fit into the capsule. I would go to the sulcus. Since this lens is not designed to put in the sulcus, I think the surgeon should go to a different lens.

DR. McMAHON: Thank you. The second you mentioned that is a biconvex optic. Is it a bispheric optic?

DR. BREEN: Michael Breen again. It is biconvex and bispheric, yes.

DR. McMAHON: Thank you.

CHAIRPERSON WEISS: I'm sorry. Do you have another one?

DR. McMAHON: One more. That is, you indicate in your surgical protocol to use for atropine on two occasions, post-op and immediately

post-op. Is there specific justification for that? Is there evidence of that as a requirement?

DR. SLADE: The theory -- Stephen Slade again. The theory with the CrystaLens was to atropinize the eye to give the polyamide haptics a chance to be sealed down as a capsular bag seals down. We wanted to put the eye at rest during that.

We initially started out with a week to two weeks of atropine and have cut it back to once at the time of surgery. The recommendation would be once at the time of surgery and then on the first day.

DR. McMAHON: I understand the principle. I was asking if you actually have any data or evidence to suggest that it makes any difference at all.

DR. SLADE: Have we implanted -- okay. To that we would have to implant CrystaLens without atropine. I don't believe that was done.

DR. GORDON: Judy Gordon. This was not

assessed in a controlled fashion but there was early experience outside of the U.S. suggesting that the atropine did provide some benefit and allowed the lens to position in posterior fashion without an early movement.

DR. McMAHON: Thank you.

DR. SLADE: I'll just add one more comment. In sites outside the U.S. where it was not followed -- the atropine protocol was not followed, the results were not as good. Interestingly not our own studies but other investigator studies of plate haptic IOLs with atropine in mimicking this protocol did not achieve an accommodative effect. It does have to do with the specific lens and the atropine does seem to make a difference.

CHAIRPERSON WEISS: Mr. McCarley.

MR. McCARLEY: I just have two quick questions. Can you describe the control population a little bit better whether or not these were similar type lenses or whether these were completely different type design lenses? No. 2,

did you see any differences in the amplitude of the accommodation in the power ranges that you were using in this study?

DR. BREEN: This is Michael Breen. In relation to the standard IOLs that were used in the substudy there was a variety of IOLs and a variety of material so it wasn't one specific lens. All of the lenses were 6 millimeter optic sizes with the exception of four that were 5.5 millimeters.

MR. McCARLEY: So they weren't plate haptic type lenses? They were standard 6 millimeter and so forth?

DR. BREEN: Yeah. There were no plate haptic lens in that substudy group.

MR. McCARLEY: The second question was whether or not there was any difference in the amount of accommodation you saw in different ranges of powers.

DR. SLADE: Stephen Slade again. We did look at that and there was not. Whether that is a combination of the different powers, the higher power lenses being in a different length of an eye

and that equalizing out, it did not seem to make a difference. One update in the 10 patient substudy. You asked the question about YAG. There were no YAG capsulotomies in that group from Dr. Dill.

CHAIRPERSON WEISS: Dr. Ho.

DR. HO: Congratulations on some concise presentations this morning. Intervention bias is always dangerous either from the subject receiving a procedure or a drug, or from the standpoint of an evaluator of an outcome. Can you just clarify in my mind to what extent masking was used?

DR. BREEN: This is Michael Breen. This was not a mast study.

DR. HO: Okay. Specifically I was thinking about the contrast sensitivity measurement. All patients that in your comparison groups, for example, with CrystaLens versus heterogenous group of posterior chamber lens implants knew that they were in separate groups at the time.

DR. BREEN: That's correct.

DR. HO: Okay. One of the exclusion

criteria, going back to inclusion, exclusion was age-related macular degeneration. What was the definition of that for clinicians that were normal patients?

DR. GORDON: Judy Gordon. There were no specific criteria. It was really a clinical judgment but there was a requirement for best potential acuity of 20/32.

DR. HO: And that was established by?

DR. GORDON: I think a potential acuity meter. Also just to note as an added note, typically in clinical trials of intraocular lenses there would be an analysis of best case cohort versus worse case assuming that postoperatively you would note additional cases.

But I think in screening the patients for best potential acuity, there were a very small number of worse case patients and, for that reason, we analyzed the entire cohort. I think there were under 15 cases postoperatively so we decided to include every one.

DR. HO: I appreciate that, and the fact

that there was no difference between best and worst.

Another question I have with respect to potential retinal contraindications for this. I would agree that in most of these senior patients the vitreous -- you don't want to think of this as a vitreous face movement because it is essentially water in the operating room. I could believe a hypothesis of just pressure.

One of the exclusion criteria was progressive ocular degeneration. I think about high myopes for an excessively large eye. Were they excluded, per se, and, if so, what were the parameters?

DR. SLADE: Stephen Slade again. They weren't excluded per se but the lens power range that we had, we had a limited range of manufactured power so, indeed, we didn't do high myopes or high probes on either side because the powers weren't manufactured.

DR. HO: Thank you.

CHAIRPERSON WEISS: Dr. Bradley.

DR. BRADLEY: The sponsor finished with a very simple statement and simple conclusion. In the summary they stated that the CrystaLens was designed to provide patients with the full range of clear vision without glasses. I emphasize the notion of clear vision. The conclusion made by the sponsor was that the lens has succeeded in doing this.

But it is clear from the acuity data that although these patients generally are 20/20 with their best corrected distance correction while looking at the distant target, I think it approaches 100 percent of them -- in order to get 100 percent meeting a criteria, we have to drop it to 20/40 at near.

It's pretty clear that if they are 20/20 at distance and 20/40 at near, they don't have clear vision. I just wondered if I am interpreting that correctly. The sponsor thinks that they have shown that the lens provides a full range of clear vision even though the acuity drops at near. Just a clarification on that.

DR. GLASSER: Adrian Glasser. That is certainly an accurate assessment of the results. The CrystaLens is designed to provide a certain amplitude of accommodation. The claim is not that it is producing 5 or 6 diopters that a young human eye might be capable of. Perhaps were a lens to achieve that, then one could assess the near acuity to a level of 20/20.

In this case the claim is that the lens is producing perhaps a diopter or so more than a standard IOL. On that basis I think it's a reasonable realistic claim that the functional vision is provided to some degree at distance intermediate and near.

DR. BRADLEY: I think that's right. I think that it is very important because of the uncertainty about language here. We have had the sponsor describe to us many definitions of what accommodation is and it is pretty clear that even within the expert scientific community there are certain disagreements about what accommodation is.

The language that we use here today and

the product should include be very clear. When making a summary statement that the product has provided a full range of clear vision, I think this is a bit misleading because most people would interpret that as clear meaning focused.

It's pretty clear from the data that it does not provide a full range of focus or clear vision. I think just to remind everybody that we need to be very clear -- very clear and focused on this issue.

CHAIRPERSON WEISS: I think that is something that the panel can address in labeling from the erudite patients that you must have in your practice who are reading the Blue Journal at a 98 percent rate --

DR. SLADE: Our waiting room is full of it.

CHAIRPERSON WEISS: -- I notice that things then drop down to 77 percent patients saying they could do most things. Then 57 percent of patients saying they could read the newspaper and 38 percent of patients saying they could do

needlework. I guess it depends if you have an erudite practice or a sort of stay-at-home-mom practice.

DR. SLADE: Yeah.

DR. GORDON: This is Judy Gordon. Perhaps I could add a response to Dr. Bradley's very valid comments that the indication for use is specific to providing near, intermediate, and distance vision. I think some of the language used here is to provide a sense of what we think the lens is doing, that the indication is quite clear as well in what the patient might expect.

DR. SLADE: Stephen Slade again. Just one thing. What is a definition of clear vision? The majority of the patients choose not to use their spectacles so, to me, they are choosing then this vision with just this lens rather than any augmentation so it's clear enough.

The other thing is that compared to what as no other aphakic solution currently affords anywhere close to this amount of range of vision. I think that is a large improvement.

Just one last comment. It is important to differentiate this from a multifocal IOL. Multifocal IOL theoretically would provide peaks of vision but not more of a functional vision.

A multifocal IOL I would disagree with it being able to be called accommodating because a multifocal IOL presenting multiple images to the retina whereas this is simply presenting one image at a time or one focus at a time. Thank you.

CHAIRPERSON WEISS: Dr. Coleman, do you have any questions? Otherwise, I'm going to go around for a second go-around.

Dr. Matoba.

DR. MATOBA: Well, one side. I don't think that erudite and stay-at-home moms are virtually exclusive.

CHAIRPERSON WEISS: I stand corrected.

DR. MATOBA: Okay. Now, moving on my question is my concern about the 4.5 millimeter optic. You had did the contrast testing and you have a patient satisfaction surveys saying that they do not have more glare.

These were older patients, all over than 50, and they tend to have smaller pupils. Do you have any data where you have stratified this information by pupil size because they did see the range was up to 7 millimeters in your contrast sensitivities.

DR. GORDON: The analysis was -- Judy Gordon -- performed to assess the effect of pupil size and there was no effect on the contrast sensitivity outcomes by pupil size.

DR. MATOBA: And patient satisfaction in terms of a glare or seeing a lens edge or things like that?

DR. GORDON: Those data were not stratified by pupil size. I think we felt that in conducting fairly well controlled contrast sensitivity study with a glare source was a more definitive way to assess the effects. For that reason we chose control lens as patients implanted with control lenses with larger optics.

CHAIRPERSON WEISS: Dr. Ho.

DR. HO: Based on this confusion of the

definition of accommodation and the mechanism, my suggestion and what I anticipate will be some round-and-round discussions later which could save some time would be an agreement to eliminate the word accommodating from the description and it might actually simplify the issue and allow us to focus on what is clinically meaningful for the patient; that is, visual function.

CHAIRPERSON WEISS: I think that's going to be a determination made by the panel on the basis of the data in terms of the panel discussion and labeling whether, indeed, the panel feels that this does prove accommodation or not.

If there are no other questions, I just have --

DR. YOUNG: I guess I would perseverate on sort of the physical mechanics of this IOL. In an effort to aid the cataract surgeons using your implant in the field, could you provide some rationale for why 12 weeks post-op is the first time a YAG capsulotomy should be performed especially since there is no issue with the YAG --

I'm sorry, the posterior capsule being intact?

DR. SLADE: Stephen Slade again. The 12 weeks is what is standard for plate lens. This lens will fixate much better and is much more stable than a plate lens but that is simply from a plate lens guidance. In the field it might turn out that you don't have to wait that long.

DR. YOUNG: I see. Okay. Would you recommend perhaps that this be a comment that the effects of performing a YAG capsulotomy prior to 12 weeks are unknown for this particular lens?

DR. SLADE: Yes. We don't know the effects of doing that so that is correct.

CHAIRPERSON WEISS: I have one final question and then we will take a 15-minute coffee break. You have a chart of 78 percent of primary eyes had 20/40 or better uncorrected distance and near and this increased about 18 percent and 96 percent with bilateral subjects.

How do you account for the discrepancy of the marked improvement of the visual acuity uncorrected when they had bilateral? Would that be

that if you had a unilateral lens placed in the second eye and the surgeon got a capsular tear, would that patient be impaired because they couldn't get the lens placed in the second eye? I think it's page 17 of the presentation.

DR. GORDON: This is Judy Gordon. Although this is better answered by a clinician, I will comment that in all of these analyses and having been involved in many studies of vision correction, bilateral outcomes are generally substantially better than unilateral.

However, I think the consensus and the data that we have generated here suggest that even in patients in whom only a unilateral implant may be allowed if they have previously had another type of lens, or if a fellow eye that is later operated on is not -- you know, can't be considered for this lens, the outcomes are still good for unilateral implants. We are simply showing that it is improved with bilateral implantation.

CHAIRPERSON WEISS: Dr. Grimmett and then Dr. McMahon.

DR. GRIMMETT: Mike Grimmett. In follow-up to a comment by Dr. Slade earlier, he was commenting that the CrystaLens situates posteriorly approximately 8 millimeters back from the corneal plane which gives it an effective IOL optical zone of 5.4 millimeters at the pupillary plane.

I want to know about that 8 millimeters posteriorly. Did that differ in myopic versus hyperopic eyes and just intuitively thinking that a hyperopic eye everything would be closer together and would they then, therefore, have an effective optical zone at the pupillary plane. Is that true or false and did the lens situate differently in hyperopes versus myopes.

DR. SLADE: All of the calculations, theoretical calculations, as to the actual position and as to the optical zone, we did not see a difference when we looked at myopes versus hyperopes, lens powers versus lens powers, but theoretically, yes. The father back it was situated, the larger the effective optical zone that would be projected on the cornea.

DR. GRIMMETT: Mike Grimmett again. Then it would logically follow that a high hyperope with less distance from the lens to the anterior corneal surface would then possibly have a higher risk of glare with dim illumination mydriasis, and things like that?

DR. SLADE: Well, we didn't see that. That might be balanced by that being a more powerful lens, the high hyperope pupil in general than myopes but we did not see that.

DR. GRIMMETT: Thank you.

DR. GLASSER: May I just make a correction? Adrian Glasser. The number that you just mentioned, 8 millimeters posterior, that is not correct as far as I'm aware. The actual placement of the lens should be approximately 5 and half to 6 millimeters posterior of the cornea. Eight sounds a little --

DR. GRIMMETT: I'm referencing page 160 of 195 under Tab 11, contrast sensitivity in Vol. 1. I'll let you turn to that page. On page 160 at the bottom, four lines from the bottom, it says the

IOL position is 7.95 millimeters from the anterior granial surface.

DR. GLASSER: Adrian Glasser again. I think that number was taken from Stewart Cumming's published paper with plate lenses, not necessarily data from the C&C Vision CrystaLens.

DR. GORDON: We have just confirmed -- Judy Gordon -- that is published data. That was provided as background in this section of the PMA was not data generated specifically on this lens.

DR. GRIMMETT: So then if the lens does situate closer than that figure, those calculations on pupillary diameter to over estimate the optic size would also change, that is correct. The 5.4 figure -- the 5.4 millimeter effective optical zone at the pupillary plane is also incorrect, that this lens sits closer to the cornea.

DR. GORDON: I think those measures are based on calculations but not in vivo data generated from patients with the CrystaLens. I think this reference that you are describing says 7.95 millimeters is published data on plate lenses.

DR. GRIMMETT: Okay. And then in the studies where you did do ultrasound or whatever mechanism you determined, where does the CrystaLens sit in the very few patients that you have? If it's not 8 in the couple that you, what is it?

DR. BREEN: Michael Breen again. In those patients the anterior chamber depth measurements ranged anywhere from 5 millimeters to 6 millimeters. Now, those measurements refer to the distance from the back of the corneal surface to the anterior surface of the lens. These calculations that were cited from Dr. Cumming's literature took into account changes in vitreous chamber depth which refers more to the posterior surface of the lens.

CHAIRPERSON WEISS: Dr. McMahon.

DR. McMAHON: Getting back to your question, Dr. Weiss, in addressing the binocular vision. In addition to the concept of binocular summation, I would suspect actually that the fact that the first eye of the binocular patients the surgical instructions were to target to minus a

half, and the second eye to use the results of the first eye to aim for plano.

Under those circumstances that alone potentially can account for that improvement in uncorrected vision. Does the sponsor agree?

DR. SLADE: Yes, we would agree with that.

CHAIRPERSON WEISS: Just another follow-up on that question and then we will break. When you think there might be any issues if the patient had a standard PCI well in a fellow eye and the CrystaLens in one eye, what would they be using for their near vision? Would they just be using monocularly with the CrystaLens? Would they be using specs? What do you anticipate?

DR. SLADE: Stephen Slade. I'll take a stab at that. Theoretically, I think it would depend on which lens was placed in the dominant eye and which was placed in the non-dominant eye. I think it would also depend upon what the refraction on it was.

I believe they would be using the

CrystaLens -- we have no data for that. I believe they would be using the CrystaLens for the range, but I think it would largely depend upon their resting refraction and which was the dominant and non-dominant of each lens.

CHAIRPERSON WEISS: In your data it was mentioned that about 4,000 cases have been done outside the United States. I have a page but I don't want to waste anyone's time. For the cases that have been done outside of the U.S., do they have any information as far as unilateral on the implantation with PC IOL on the other one?

DR. GORDON: Judy Gordon. I don't believe that number has been implanted outside the U.S. but I would have to look it up. We haven't collected that information specifically.

CHAIRPERSON WEISS: Fine. I think we are all set with the question period and we are going to break for 15 minutes. Let's all meet back here promptly to begin the FDA presentation at that point.

Judy, I'm sorry. Hold on one second.

DR. GORDON: Thank you for calling me. I just wanted to respond to Dr. Grimmett. Unfortunately the survey case that you were looking at was an older survey that was eliminated. It's in stay in the penal pack. If you look at page 153 in Vol. 1, I think you will see the analysis that you are looking for.

DR. GRIMMETT: You are referring to Table 10.7?

DR. GORDON: Tables 10.6 and 10.7. They are slightly different.

DR. GRIMMETT: Yeah, I saw there were different.

DR. GORDON: This particular question proved to be extraordinarily confusing to us and to the patients and so a different question was substituted.

DR. GRIMMETT: Too bad. I liked that other question.

DR. GORDON: Very hard to answer for a mean age of 70.

CHAIRPERSON WEISS: Actually, I'll just

mention in terms of follow-up, I think on page 7 in the blue book it says 4,000 units have been distributed. I read that as implanted.

We now will break for 15 minutes.

(Whereupon, at 10:25 a.m. off the record until 10:40 a.m.

CHAIRPERSON WEISS: I'm told the sponsor had a brief clarification they wanted to make and then after Judy Gordon makes that clarification, we will then start the FDA presentation.

DR. GORDON: Thank you very much. Judy Gordon. Just two answers -- one clarification and one answer. Two patients enrolled in the study did undergo YAG capsulotomy before 12 weeks, between one and two months. Those capsulotomies were performed safely and the patients had good outcomes.

The second is a clarification for Dr. Ho. In fact, the contrast sensitivity testing was performed by mast examiners at each site. The patients were not masked because they knew if they had an investigational lens or a standard lens.

All of the examinations were done in a masked fashion. Thank you.

CHAIRPERSON WEISS: Thank you. I'm going to ask to begin the FDA presentation.

Dr. Lepri, are you going to start, or Donna?

MS. LOCHNER: I just have a few brief introductory comments.

To introduce this PMA I would like to focus my comments on the additional claims that C&C Vision proposes for their CrystaLens IOL which the sponsor designates as an accommodating IOL.

For the purposes of this discussion, additional claims are the extraordinary statements of clinical benefit that are contained within the labeling, particularly in the indication section of the labeling.

As you know, most IOLs are indicated for primary implantation in the capsular bag for the visual correction of aphakia following cataract extraction. The C&C IOL also is indicated for patients who may benefit from improved near,

intermediate, and distance vision without spectacles.

A central issue for your review of the extraordinary claims made by the sponsor is whether you believe that the near and intermediate visual acuity data and limited other objective outcomes as discussed earlier by the sponsor adequately support the claim of accommodation.

We ask that you concentrate on the clinical and technical merits of the claims and not necessarily on the exact wording to be placed in the labeling. We are happy to receive any specific wording you may feel is important but in any instance where you do not have strong preference, we can work through wording issues at a later time.

At this time I would like to acknowledge the work of the FDA review team. Don Calogero performed the team leading and engineering reviews. Bernie Lepri and Gene Hillmantel did the clinical reviews.

Susanna Jones is the toxicology reviewer and Susan Gouge, microbiology. Valerie Flournoy

performed the Good Manufacturing Practices Review. Sybil Wellstood from Bioresearch Monitoring. And Jack McCracken reviewed the patient labeling. Now Dr. Lepri will present the FDA clinical review.

DR. LEPRI: Good morning members of the panel, representatives of C&C Vision, FDA members, and guests. I would like to begin by commending the sponsor on a well-prepared document and their incomparable cooperation with the FDA in preparing for this panel meeting.

I am then going to present to you FDA's questions regarding this application but before I begin, I would like to give a special thanks to Dr. Gene Hillmantel for his assistance to me in providing statistical and clinical interpretations of the statistical analyses that he performed on the accommodative substudies performed by the sponsor.

In preparation for addressing the first question, we would like the panel to take into consideration some information that is very germane to the fundamental objective of the indication of

this device, the achievement of near visual acuity through accommodation.

Outside of the requirements of protocol was conducted additional testing in an effort to document the mechanism of action of the CrystaLens. That is accommodation achieved by the forward and backward movement of the lens optic along the axis of the eye.

This testing included dynamic retinoscopy, defocus, near point evaluation, near vision through the distance Rx with cycloplegia, power mapping with the Tracey wavefront aberrometer, and anterior chamber depth analysis through A-scan. It is important to note that both cyclopentolate and 6 percent pilocarpine were utilized in the studies.

The accommodative substudy summary data is presented in the following chart. This table presents the summary of the accommodative substudies and one can see that there is a wide spread in the dioptic results measured ranging from 0.72 diopters to 3.14 diopters.

The .72 diopters was measured by the Tracey aberrometer and in dynamic retinoscopy a very subjective technique that was measured to be an average of 3.14 diopters.

Analysis of the correlation among these various forms of measurement of accommodation reveals that the highest correlation among these findings is between the Tracy aberrometer and the change in anterior chamber depth as measured in diopters that correlation being 0.662. The lowest correlation is a negative one, that being between dynamic retinoscopy and aberrometry of minus 0.54.

Question No. 1. This is the first IOL that proposes accommodation as its mechanism of action. (a) Do the effectiveness data support a claim of accommodation? (b) What performance issues should be considered both generally and for product labeling?

Information for question No. 2. The stability of the CrystaLens hinge was demonstrated by in vitro dynamic fatigue testing up to one year and analysis of change in the distance manifest

refraction spherical equipment between consecutive examination and (c) if by intermediate visual acuity between consecutive examination.

The stability of the MRSE of primary eyes is presented in the following table. One can see that on the average that 85 percent of the primary eyes were within a half diopter and 96 percent were in the range of one diopter, the distance manifest refraction spherical equivalent when the measurements were made between form three to four and from form four to form five.

The mean difference from the form three to form four interval was minus 0.03 with a standard deviation of 0.52. From form four to form five the mean difference was 0.13 plus or minus 0.45. I believe that was for the one diopter.

It then went on to analyze the stability of the uncorrected near visual acuity. This table presents those results for the one year consistent cohort. Approximately 81 percent for either form three to form four and form four to form five were within one line of acuity as measured between those

consecutive intervals.

Approximately 13 percent of the form three to form four interval had an increase of greater than or equal to two lines and at form four to form five 14.5 percent had an increase greater than or equal two lines.

The intermediate visual acuity analyses through the distance correction for the United States eyes is presented in the following table and is stratified by primary eyes and fellow eyes. Approximately 80 percent of primary and fellow eyes were 20/20 at intermediate test distances at one year and 95 percent were at 20/25 or better by one year.

Question No. 2. Considering the previous data I presented to you, do you believe that the sponsor has demonstrated the stability of the hinge and, therefore, the stability of the accommodative refractive effect?

Question No. 3. Does the panel recommend any other modifications to the proposed (a) physician labeling, and (b) patient labeling.

Question No. 4. Do the data in PMA P030002 support the proposed indication statement as follows: Primary implantation for the visual correction of aphakia in adult patients with cataracts provide improved near, intermediate, and distance vision without spectacles. Thank you.

CHAIRPERSON WEISS: Thank you, Dr. Lepri.

We will now have a 10-minute session for questions to Dr. Lepri from the panel. No questions?

Dr. Lepri, thank you very much for a very clear presentation.

We will proceed onto additional comments from the sponsor if they have any.

DR. GORDON: Thank you. Judy Gordon, representing the sponsor. We have no additional comments at this time. We will have some closing comments but we would like to thank the panel and the FDA reviewers for working with us from the beginning of this IDE to get to this review of this PMA. Thank you very much.

CHAIRPERSON WEISS: Thank you.

In that case, we will then move things up a bit and go on to our panel reviewers and begin with a presentation of the primary panel reviewer. First we'll start with Dr. Arthur Bradley and then go on to Dr. Anne Coleman.

EXECUTIVE SECRETARY THORNTON: Dr. Bradley, would you prefer if Dr. Coleman went before you? Do you need some more time?

DR. BRADLEY: We were going to test this out over lunch but it might work. If it works, we're ready to go.

CHAIRPERSON WEISS: Mr. McCarley has a question for Dr. Lepri so while we are setting up, you can do that.

Dr. Lepri, Mr. McCarley has a question.

MR. McCARLEY: Rick McCarley. I had a question for Dr. Lepri. When I'm reading the indications for use, I just wanted to be clear because my understand -- I just want to be clear about my understanding of this.

It's for the primary implantation for the visual correction of aphakia in adult patients with

cataracts. Then the additional portion is provide improved near, intermediate, and distance vision without spectacles.

Just for clarification, should the first portion be primary implantation for the distance correction of aphakia which is a typical intraocular lens indication? Then it would be to provide improved near and intermediate vision?

DR. LEPRI: This is printed here in this slide as the sponsor had it printed in their application.

MR. McCARLEY: I see.

DR. LEPRI: That's why we bring it to your attention now for consideration for later.

MR. McCARLEY: Just a piece of clarification. Thanks.

CHAIRPERSON WEISS: Dr. Bradley, would you mind if we start with Dr. Coleman perhaps while you're setting up?

DR. BRADLEY: Not at all.

CHAIRPERSON WEISS: Do you have any computer work?

DR. COLEMAN: No.

CHAIRPERSON WEISS: Fine. That sounds excellent.

DR. COLEMAN: I'm very low tech.

CHAIRPERSON WEISS: The benefit of no computer these days. We are going to start with Dr. Coleman as actually the revised schedule does show.

DR. COLEMAN: Thank you. I was going to basically summarize my review. In terms of reading the question: This is the first accommodating IOL to be reviewed by the panel.

Do the effectiveness data support a claim of accommodation? Are there any issues related to the accommodative performance of the CrystaLens that you believe should be considered either in general or for inclusion in the device labeling?

Although there are different definitions of accommodation, I felt that the effectiveness data did appear to support a claim of functional accommodation for the CrystaLens since

approximately 80 percent of primary eyes had uncorrected distance acuity and uncorrected near acuity of 20/40 or better.

In addition, because eyes within plus or minus half diopter of plano were more likely to have a distance acuity and near acuity of 20/40 or better, and because fellow eyes which were targeted for plano had a greater frequency of uncorrected distance acuity and near acuity of 20/40 or better, I recommend changing the device labeling on page 2 for aiming for plano instead of minus half sphere, although the recommendation for the clinical trial was to aim for half sphere correction.

In addition, the changes in the MSRE from postoperative months one to two to months three to six, and for months three to six to months 11 to 15 are very relevant. Although approximately 96 percent of eyes had a change of distance acuity of less than or equal to plus or minus one diopter, I am concerned by the large range and the acuity difference between the postoperative visits.

Because a change of plus or minus one diopter

is felt to be relevant, I recommended presenting the data as the percent that it changed as less than or equal to plus or minus 0.50 diopter or half diopter.

Including this information in the device labeling I felt would help surgeons when evaluating this and also including the distance and near acuity would also be helpful in evaluations by the surgeons. This recommendation was done in the rebuttal.

The next question was to demonstrate the stability of the hinge design of the CrystaLens. I'm going over the in vitro dynamics fatigue test and whether I believe that the sponsor had demonstrated the stability of the hinge and, therefore, the stability of the accommodative refractive effect.

I did some calculations assuming that the device fatigued at one million cycles. At that it looked like you might only have 10 years of accommodative ability or of flexibility of this device.

I felt that it was important to indicate in the labeling that this device may have a limit in terms of it's flexibility and its ability to give a range of different acuities without correction for individual patients and the surgeon could evaluate that.

The uncorrected near acuity appeared relatively stable. Approximately 80 percent of eyes had a change in acuity with one line of acuity and approximately 12 percent had an improvement in their acuity from postoperative months one to two to three to six months. And then from three to six to 11 to 15 months approximately 79 percent had a change in acuity with one line, and approximately 16 percent had an improvement in near acuity.

I did not find any data on the difference in intermediate visual acuity between consecutive examinations. Then I also repeated my comments on the MSRE related to question one.

In terms of providing recommendations for modifications or additions to the labeling, recommendations that I had were that a warning

precaution that the effect of vitrectomy on accommodative performance of CrystaLens is unknown.

Include information from the patient's survey (Table 10.3) in the labeling. This information is important for a surgeon's discussion with potential patients regarding their expectations.

Mention range of axial length and lens powers that were used in the study in labeling under precautions. Those axial length were 21.0 to 26.6 millimeters and lens powers of 16.25 to 27.5 diopters.

Mention that atrophy sulfate 1 percent should be given immediately postoperating and postoperative day No. 1 on page 2 of labeling since this is how the clinical trials were done.

Mention possible increased rate of CME associated with sulcus-bag placement of haptics under adverse events.

Then in summary, I was asked, Do you believe that the data in the PA provide reasonable assurance of safety and effectiveness? I felt that

if the above additions and modifications to the labeling are done in addition to those that we recommend today, I believe that the data in the PMA would provide reasonable assurance of safety and effectiveness.

CHAIRPERSON WEISS: Thank you, Dr. Coleman.

Dr. Bradley.

DR. BRADLEY: Sorry for the technical problem. I guess this will all be done with when Bill Gates buys Mackintosh.

As some of you know, I have been working for the FDA for some time reviewing all sorts of products that have no personal relevance to me. Finally we have one that is going to provide people like myself with accommodation in the aging second half of their life.

I am quite excited by such a product, let me tell you. I want to formally announce to the public record and to the FDA that this is absolutely the last PMA that I will review without a reading add.

So let's see if we can get through this. We all know the product. As usual, I usually spend most of my time discussing the effectiveness of the product. I really try to narrow it down to three questions.

Does it allow the eye to accommodate and by how much? What is or are its mechanisms of action? This is certainly pertinent when it comes to labeling. And does it provide adequate quality near vision? I think those are the three keys issues we have to deal with regarding effectiveness.

It's worth reiterating the really unique claim that this product has. This IOL employs the eye's natural accommodated mechanisms to alter the axial position of this IOL and in doing so alter the power of the eye. We will call that accommodation.

Effectiveness concerns. Those of you who read my review are aware that I have a few concerns. Let's go through them. Concern No. 1, does the lens as claimed provide active

accommodation and, if so, how much? This is really the most interesting question of the day.

I looked through obviously a very lengthy document and tried to narrow down the key points to one panel here. Let's list them as evidence for accommodation.

Right at the top I put in my own bias. I like to see objective data where possible. We have objective data. This was obtained with a new type of autorefractor called Tracey on five subjects, 10 eyes. One eye was seen like a clear outlier so I've reduced it to nine eyes.

They observed the difference in refraction between an eye with pilocarpine in it and the same eye at a different time with cyclopentolate. The difference was on average slightly less than half a diopter. This indicates that one can obtain a pharmacologically induced accommodative amplitude of slightly less than half a diopter.

Second, the barometry is particularly important because it not only tells us something

about the change in the power of the eye but also the mechanism. As you know, the proposed mechanism of this particular product is that the eye well will move anterially and, in so doing, will produce an increase in the overall power of the eye.

Again, 10 subjects -- five subjects, 10 eyes. Again, data were taken with the eye having cyclopentolate in it and with pilocarpine in it. Under those two conditions the difference in the anterior chamber depth was about .65 millimeters. We can conclude that we pharmacologically induced accommodation. We have about a .65 millimeter movement of the lens in anterior direction.

As Dr. Glasser pointed out to us, that is, in fact, the whole principle behind this lens. This is data to support that, in fact, it does work as designed.

How much accommodation should that produce? Well, it depends a little bit on the actual positioning of the lens and the power of the lens, but let's say about one diopter and would be indicated by that study.

Another really quite interesting study. In this case it was 126 subjects. I think it was made with the contrasensitivity substate. They do what is called a near over refraction, and that is we want to find out how much extra power do we have to add in order to get the near acuity to maximum.

The evidence from that study indicates that about 1.1 diopter of accommodative power provided by this IOL. How do I come to that result? The difference between the near over refraction of the control group which is a standard IOL and that of the CrystaLens group. The difference between those two is about 1.1 diopter.

The difference between those two groups presumably is that the CrystaLens group were accommodating. Therefore, the difference in the over refraction power is an indication of the accommodative amplitude, slightly over one diopter.

We have two datasets. Again, this is on the small substudy of five patients. We've 10 eyes each. Dynamic retinoscopy indicating over 3

diopters of accommodation. Clinical depth of focus study indicating approximately 2.5 diopters of accommodation.

Both of these methods are notoriously difficult to do precisely. One has to wonder how come when the three previous measures are indicating between a half and one diopter these two measures are indicating between 2.5 and 3 diopters.

Next down the list. We end up now in the major part of the submission which involved visual acuity measurements. By the way, these are extremely difficult to interpret in terms of evidence for actual accommodation. I have tried to summarize it in the following way.

First off, let's consider the intermediate visual acuity data through the distance correction. In this case we've got 368 samples. What was the intermediate distance? It was 80 centimeters or 1.25 diopters.

It turns out through the CrystaLens the patients mean visual acuity at intermediate distance was about 20/20. Although I couldn't find

it, I presume this is the same as the mean acuity of these patients at distance through the distance correction.

That is, their intermediate acuity was basically the same as it was at distance which is exactly what we would expect if the eye was accommodating, or able to accommodate, 1.25 diopters. The evidence from that visual acuity study is that it looks as though the lens is providing 1.25 diopters of accommodation.

What about the near acuity? Much talked on. Near acuity was obtained at 40 centimeters. That's a 2.5 diopter at demand. The near visual acuity through the distance correction, again 369 eyes, the mean acuity was 20/37. Clearly acuity has dropped when you went from the 80 centimeters to the 40 centimeters.

Why has it dropped? There is one obvious reason. The image is now out of focus. It is clear then from these data that the CrystaLens does not provide 2.5 diopters of accommodation. There is no doubt about that.

My estimate from these data is that it is providing about one diopter of accommodation. How do I come up with that number? Again, I am having to speculate a little bit because, like I say, these data are very indirect ways of estimating accommodation. The basic way I come up with this number of one diopter is the following.

If we look at the control group that we studied with the standard IOL, presumably these patients have no accommodating amplitude whatsoever. At intermediate distance they had on average an acuity of 20/27. Presumably at this intermediate distance they were 1.25 diopters defocus.

Under the test conditions of the study, it looks like 1.25 diopters of defocus gives an acuity of 20/27. At near the patients with the CrystaLens had an acuity of 20/37. The presumption is they are out of focus by more than 1.25 diopters.

Let's say 1.5 diopters. So if they are out of focus by 1.5 diopters and the target was 2.5

diopters, that means they could perhaps accommodate by about one diopter. That's how I come up with that number.

So I put together the objective autorefractor data, the biometry data, the near over refraction, the intermediate and distance acuities through distance correction, and they all seem to point to between .5 and one diopter of accommodative amplitude provided by the CrystaLens. When I say accommodative amplitude, I mean that the eye is able to increase its optical power by between a half and one diopter.

The unfortunate thing is that the two most compelling sets, the top two, objective autorefractor and the biometry data were only carried out on five subjects. Rather than obtain these data while the patients made an accommodative effort, they were obtained by taking the difference in the data between pilocarpine and cyclopentolate.

It turns out that is far from idea. In the end my provisional conclusion is indeed the CrystaLens does seem to generate between half and

one diopter of extra power and, thus, we can conclude that it does show evidence of accommodation.

Let's move on to the next effectiveness concern No. 2. This is one of mechanism. Like I say, this is quite important when we come to labeling. Does the CrystaLens generate extra optical power in the eye by moving forward as claimed while the patient looks at a near target?

As I just mentioned, the biometry data will keep for this mechanistic question. The biometry data absolutely show that the lens did move forward. Remember, it was only 10 eyes. The eyes were compared under these two pharmacologically induced conditions. One with cyclopentolate and one with pilocarpine.

So, as I said, this is far from ideal. Both drugs affect the action of the ciliary muscle and that's the reason for using them in this case. But it's very important to appreciate these drugs also affect the iris muscles and that's these two anterior chamber measurement were made with

unnatural pupil sizes and may have been an influence by the extreme dilation and contraction of the iris. My recommendation is the biometry measurements should have been made while subjects viewed distance and also near targets and the difference between those two measurements taken. That would have been much more compelling. We would have had evidence that, in fact, the CrystaLens does move forward during attempted accommodation. At the moment we don't quite have those data.

Provisional conclusion. The CrystaLens can move axially as designed but we have no evidence that it does so during near work which is unfortunate.

Effectiveness concern No. 3. Does the lens provide sufficient near vision quality to eliminate the need for a reading add. This is really, I think, the strong suit of the sponsor coming in. They have collected lots of data on visual acuity at near, at distance, intermediate. In fact, most of their effort was placed on this

sort of data collection.

They have used the visual acuity data at near in particular as evidence that the lens is accommodating. They have encouraged us to accept these visual acuity data as evidence of accommodation focusing our attention on not necessarily the mechanistic activity of this lens but on the end result.

Does it really work for the patient? I think that is a reasonable approach. I have taken that approach here and come up with a concern. See what you think.

In my previous analysis on amplitude of accommodation estimates, again I came up with estimates ranging from half to one diopter from their data. We can ask whether this is sufficient to provide functional vision ethnia. How do we answer that question? There are lots of ways one could. I had a look at the literature and came up with the following.

Typically patients request near adds during their early to mid-40s when accommodative

amplitudes are about one diopter. This analysis suggest that the extra power provided by the CrystaLens may not be sufficient and patients may still require a reading add.

How do I come up with that? The idea is very simple. If they have -- if the lens provides perhaps one diopter of accommodation and we find that many people require a near add when they have one diopter of accommodation, then one could suggest that maybe even though CrystaLens will give about one diopter of accommodation, that may not be sufficient to preclude the necessity for a reading add. That's the point there.

However, this is quite important because the IOL replacement is occurring at a significantly older age than the 40 to 45-year-old age group that I just talked about. The .5 to one diopter power change in combination with senile pupil miosis may be adequate for near work.

That is, having one diopter of accommodation may be adequate as long as your pupil is quite small as it will tend to -- pupils tend to

decrease in size with age. In the end for this age group maybe one diopter is adequate.

The sponsor did a patient survey and asked lots of questions. One that particularly caught my eye, and I think Jayne Weiss mentioned it earlier, is that when asked what proportion of these could read the newspaper without spectacles it was about half, 57 percent.

One presumes that is you do not need a reading add, one could sit down and read the newspaper without wearing such an add. It looks like 57 can do this.

My provisional conclusion regarding this concern No. 3 is that the CrystaLens may provide adequate near vision for about half of the patients. By adequate I mean that they can sit down and read the newspaper without a reading add.

It's worth coming back to a general concern that I think was distributed throughout my review. That is that the study design to me seemed rather odd. Here we have a product that has a very, very plausible scientific basis.

That is, that there is a lot of evidence in theory and the way that the product was designed and the way that the surgeons were trained to install the lens all seem to indicate that this lens stood a very good chance of providing old eyes with active accommodation. I mean, this is a revolution to be quite honest. I mean, I was really excited by this product.

Given all of the scientific background which leads us to think that this lens surely will work, I was really disappointed that the sponsor did not provide us with compelling data showing us the accommodative responses of an eye with the IOL in place. I was really quite disappointed about that.

Middle point there. The coupling of pupil size and accommodation is accentuated when using cyclopentolate and pilocarpine. The impact of pupil size on visual acuity is always magnified whenever the retinal image is defocused. Because of the reliance on visual acuity and the failure to control pupil size, much of the data is very

difficult to interpret.

We're not sure whether we're seeing the impact of pupil size change or the impact of power change inside the eye. That's a very, very difficult thing to separate because most influence visual acuity. I think that is, again, in all study design.

It is clear that if you are going to validate a product like this, one needs to assess changes in refraction using a controlled pupil size. Our recommendation that the FDA in the future require more compelling evidence of active accommodation, not near visual acuity, when evaluating IOLs that claim to provide active accommodation.

I think this would help the panel in the future feel comfortable that when a product claims to provide accommodation that, in fact, they have demonstrated it really does. I think that becomes particularly important when it comes to labeling. In fact, I was making this slide when the schedule was accelerated so I'm not sure what it says myself

now.

I think it is particularly important given the discussion this morning and I think Dr. Glasser did an excellent job of summarizing some of the ideas and uncertainties out there regarding even what accommodation is. It seems unfathomable that we are still arguing about what accommodation is but, anyway, we are.

I have done my own job here in another post hoc way. Hopefully Dr. Glasser will not object. I sort of tried to press multiple definitions into two types. Really there is one type which is accommodation is a change in optical power in response to a change in object distance.

When you look at a distance target, you look at a near target, the eye changes in power. It's a classic autofocus ability of the human eye. We can either have that definition with or without the mechanism.

Definition No. 2. It's the dioptic range which visual quality meets some criteria. We can have 20/40 from distance to near. That is another

type of criteria. The sponsor has preferred to use type 2 definition and by employing a 20/40 criterion the optic range spans from distance to near quite comfortably.

It's worth mentioning that although it's not true in this case, it is important to appreciate that pinhole glasses -- remember those? They used to be marketed on airplanes. I think they must have assumed that airline travelers are a bit stupid. Anyway, those pinhole glasses would also meet such a standard. It is very important to realize, therefore, thus showing what I would call the depth of focus of the eye at this criterion, 20/40, 0 to 2.5 diopter, does not mean necessarily that the eye has accommodation.

In this particular case, as I have said in that first slide, there is plenty of evidence that the eye seems to be accommodating. It is very important to appreciate that having this depth of focus with a criterion like 20/40 does not necessarily mean there is accommodation.

Okay. Finally, to the questions posed by

the FDA for the panel. Effectiveness. Although it is unclear how the lens works, it clearly provided superior near acuity compared to a standard IOL. In this minimal sense, and by minimal I mean it is better than a lens that has zero accommodation, it seems effective.

Let's continue that on. If we set the effectiveness bar a little higher, we must assess whether the lens provides adequate near vision. The analysis that I described and the sponsor's own survey data suggest that it might in some but not in others. I will call that a marginally effective product.

Issue No. 2, stability of the hinge. The hinge is clearly capable of more than 1 million movements. Again, without in vivo data it is unclear if it moves in the eye while viewing distance targets. We really don't know what's going on in the eye. It's hard to interpret the 1 million number but it looks to be a pretty stable product.

Labeling. Here, I think, it is very

tricky because of this issue of trying to communicate not only to the patient but also to the surgeons what we really mean by accommodation. The labeling should reflect the fact that the sponsor has failed to provide conclusion evidence of a mechanism of action.

There is clear evidence that this lens will not eliminate the need for a reading add in about half the eyes. The labeling should reflect this to prevent patients thinking that the lens will provide them with both a near and a distance correction.

Issue of safety. It seems pretty safe. On that point I will finish.

CHAIRPERSON WEISS: Thank you very much, Dr. Bradley. My apologies for not allowing you adequate time to finish your last slide.

We are going to -- actually, since we are moving along at a good clip, we are going to begin with the panel discussion. This may continue after lunch. We will probably break for lunch between 11:45 and 12:00.

With that said, we are going to start question by question. Would I be able to ask the FDA if they could have their questions put up there again so we can use this as a format to discuss this PMA.

While the agency is putting that up, I'll just start by verbally giving the panel the first question and then we can start the discussion before it gets put on the slide.

Question No. 1. This is the first IOL that proposes accommodation as its mechanism of action. This is a two-parter.

a) Do the effectiveness data support a claim of accommodation?

b) What performance issues should be considered both generally and for product labeling?

We're going to start with a). To the panel, do the effectiveness data of this PMA support a claim of accommodation?

Dr. Coleman, why don't we work our way around.

DR. COLEMAN: Well, after being educated

by Dr. Bradley in terms of how he was looking at accommodation, I would say yes, it does support a claim of at least one diopter of accommodation based on his estimates.

CHAIRPERSON WEISS: I think we'll use the format of sort of working our way around if no one individually has a comment on this.

DR. HO: No comment.

CHAIRPERSON WEISS: No comment. In a vote we'll call that an abstention and in discussion we'll call it a pass.

Dr. Matoba.

DR. MATOBA: Pass.

CHAIRPERSON WEISS: Dr. Bradley.

DR. BRADLEY: I get to go again? This is great.

CHAIRPERSON WEISS: Encore. Encore.

DR. BRADLEY: This is great.

DR. HO: You get my time now, Arthur.

DR. BRADLEY: Thank you very much.

DR. LEPRI: Not with all the slides, though.

DR. BRADLEY: My other 47 slides are right here. Go get your sandwiches now. You're going to need them.

Okay. Boy. I wish it were simple, you know. I think you got a sense from my presentation the frustration in trying to review a product that claims to provide accommodation with such a minimal data set providing indication of accommodation. That's a very frustrating situation to be in. I think one that we hope never to be in again. Let's summarize that again.

The objective autorefractive data, the biometry data both indicate between half a diopter and one diopter of accommodation. However, this is pharmacologically induced, not accommodation in response to a near target.

The most subjective data set was the near over refraction. This is data that is provided under non-pharmacologically induced conditions of natural viewing and it very clearly seems to show about one diopter of accommodative amplitude.

I think Dr. Glasser had a very nice slide

of that, those two histograms showing the difference between the two lenses. I think those in the end were the most compelling data set for me.

The other data set that seems compelling is the intermediate acuity data through the distance correction. Intermediate acuity was basically 20/20. For the standard IOL group this was not the case.

Again, those data seem to point to about 1 or 1 and a quarter diopter of accommodation. In the end we are left with rather incomplete data but what am I going to come down, one diopter or a half diopter? I'll saw about 1 plus or minus a quarter.

CHAIRPERSON WEISS: So you would support that it does -- the effectiveness data does support a claim of approximately a diopter of accommodation?

DR. BRADLEY: Correct.

CHAIRPERSON WEISS: Dr. Matoba.

DR. MATOBA: Well, having passed initially, but I have a question for Dr. Bradley.

The psychoplegic and the biometric data, the end was small and then you say that you have some concerns about the pupil size.

You say that the most compelling data would be the larger and the greater body of data regarding the over refraction over the best corrected distance. But if the starting point for that is a manifest refraction that was not standardized, how comfortable are you with that data?

DR. BRADLEY: I think failures of standardization as a great way to introduce noise into your data set. The noise with such a large sample size should not have affected the mean very much. I guess I'm not so concerned about that.

CHAIRPERSON WEISS: Dr. McMahon.

DR. McMAHON: With regard to that point a), I think I'm going to vote no.

CHAIRPERSON WEISS: Can you -- because of discussion can you give us your reasons?

DR. McMAHON: Sure. Dr. Bradley has actually stipulated the majority of my points so I

won't review all of them. Really all the objective evidence is all under extreme circumstances with the psychoplegic and pilocarpine. Even though the extreme circumstances we have objective evidence to maybe a half a diopter, one diopter if you go to the extreme.

All the rest of it is very circumstantial and could potentially be explained by pupil size issues, refractive issues. For example, if the examiners are instructed to push plus through in the refraction, you can account for all these differences at this point since we're talking maybe and half to one diopter.

This is a revolutionary period. This is a revolutionary device. I think the standard needs to be set that the individual or companies or sponsors need to demonstrate objectively that if they have a new process that they prove that that process really exist and I don't think they have met that requirement.

CHAIRPERSON WEISS: Just as a follow-up question, how would you propose that that get done

and what form would you like for that to get done?

DR. McMAHON: There are a variety of psychophysical methods that probably Dr. Bradley could comment on more objectively without much difficulty. I think if they demonstrate that in a follow-up study, then I would be much more comfortable believing that this truly demonstrates an accommodative effect.

CHAIRPERSON WEISS: So you might be interested in a postmarket study?

DR. McMAHON: Postmarket is probably not what we are talking about here. Almost like an ancillary study of relatively small number. There are methods that can be done.

CHAIRPERSON WEISS: Dr. Young.

DR. YOUNG: I abstain.

CHAIRPERSON WEISS: Dr. Grimmett>

DR. GRIMMETT: No comment at this time.

CHAIRPERSON WEISS: Mr. McCarley.

MR. McCARLEY: I just had one comment. That is, the definition of a standard IOL that Dr. Bradley was bringing up. I am just curious what is

a standard IOL? I would say in what I've seen here is that there is accommodation of some level but that is not to say other devices don't provide some level of accommodation.

Maybe relative to what you are defining as a standard IOL or whatever the control group was, I would agree that there is a difference. Probably measurable but I'm not sure whether you could say that overall IOLs would have an advantage.

CHAIRPERSON WEISS: Ms. Such.

MS. SUCH: I pass on this question.

CHAIRPERSON WEISS: Well, we don't have consensus and the majority of the people are passing. I would sort of like to get some feeling if we had to put it to a vote at this point under this particular question how many would vote for an effectiveness data supporting a claim of accommodation and how many would not.

Dr. Bradley, do you have a comment?

DR. BRADLEY: I don't know whether this is appropriate or whether it's a clarification

issue. Imagine that we had a product with extremely solid data indicating half a diopter of accommodation. Would we consider that effective accommodation or is the problem here that the data is inclusive, although suggestive, of accommodation? Do we have a problem here because of the quality of the data or the magnitude of the apparent accommodative effect? Either could be considered ineffective.

CHAIRPERSON WEISS: How about if I rephrased a) and said do the effectiveness data support a claim of one diopter of accommodation? Would you be comfortable with that?

DR. BRADLEY: Yeah, I think that might clarify the issue.

CHAIRPERSON WEISS: Let's make that the new a). Is that okay with the agency if we said it that way?

DR. LEPRI: Yes.

DR. ROSENTHAL: You can say anything you want.

CHAIRPERSON WEISS: That's why I like

working with these folks.

Dr. Bradley.

DR. BRADLEY: Just to make a comment on Tim McMahon's point regarding postmarket study.

CHAIRPERSON WEISS: Actually, those were my words. I think he was more interested in something earlier than that.

DR. BRADLEY: Well, perhaps I'll comment on Jayne's words then. Yeah, I think Tim McMahon is right. This is not an issue to be studied in a postmarket environment. What is missing here is not more clinical data. We've got lots of clinical data.

What is missing is some really hard core lab scientific data showing that the product does what it claims to do so we're talking about getting five people in the lab somewhere in this country or elsewhere where they can actually measure accommodation and measuring accommodation.

This is not a huge postmarket issue. It's a very focused study in the lab providing data that will generally be accepted as evidence of

accommodation.

CHAIRPERSON WEISS: Dr. Rosenthal.

DR. ROSENTHAL: It becomes postmarket if the FDA and the company and the panel agree that the lens is relatively safe and effective for the treatment of aphakia for certain indications and the claims are worked out in the postmarket arena. It depends on what the company and the FDA and the panel feel about what should be said.

CHAIRPERSON WEISS: I think what we will be able to --

DR. ROSENTHAL: Have I made myself clear to you? I mean, if you feel it's not safe and effective under any circumstances, well then it's not safe and effective. If you feel it's safe and effective for the treatment of aphakia with improved near blah, blah, blah, but the mechanism is uncertain, then you can recommend that be done either pre or postmarket.

The company and the FDA can then decide whether they want to make that determination premarket or postmarket. The claim issues can be

decided postmarket.

DR. HO: I would just echo some of those comments and expand a little bit. From my standpoint the issue of accommodation is very muddled.

I actually discounted that issue in evaluating this because I view my charge here and the definition of effectiveness is defined as reasonable assurance that in a significant portion of the population use of the device for its intended uses and conditions of use when labeled. I think that is an issue here, will provide clinically significant results.

If you ask me if the dataset of this small number of five to 10 shows evidence for accommodation I would vote no. In terms of clinically significant results, which I think is relevant in our charge here, I think that is the more relevant question. I think it is pretty compelling.

CHAIRPERSON WEISS: Dr. Coleman.

DR. COLEMAN: Maybe change the question

to, "Did the effectiveness data support a claim of one diopter of functional accommodation."

DR. HO: I'm comfortable with that terminology "functional accommodation."

CHAIRPERSON WEISS: Would the agency be comfortable with that terminology?

DR. ROSENTHAL: Whatever the panel makes a recommendation.

CHAIRPERSON WEISS: If we changed a) Did the effectiveness data --

Dr. Lepri.

DR. LEPRI: Pardon me, Chairman. Essentially that issue of one diopter of functional accommodation is addressed by Part B, what are those performance issues. Say is there accommodation and then Part B they are saying how much and you're going to put the limits on it by your recommendation so it's not really changing Part A so that is acceptable.

CHAIRPERSON WEISS: Dr. Bradley.

DR. BRADLEY: Given Dr. Glasser's comments and my own comments, I am reluctant to

invent new terms here. I would discourage the panel from adopting new terminology, although it is seemingly reasonable in this environment.

Functional accommodation sounds reasonable but, please, let's not do that. We know what we're talking about here. Do we have accommodation or do we have visual quality over the dioptic range? I mean, we can be descriptive. We don't need to add new terminology to this already muddled field.

CHAIRPERSON WEISS: So if we address question 1 by saying that do these effectiveness data support the claim of one diopter accommodation, could I have just a preliminary vote if the panel members, how many panel members would agree with that at this point? Dr. Bradley wants me to restate that. So we have Dr. Coleman, Dr. Matoba --

DR. YOUNG: Is this functional?

CHAIRPERSON WEISS: No. We've taken out the terminology. I have deferred to Dr. Bradley's sensibilities and we have taken out the word

function. We're just going to be talking straight accommodation.

If we state that, "Do the effectiveness data support a claim of one diopter of accommodation," we started on that side. Dr. Coleman said yes, Dr. Matoba said yes, Dr. Bradley said yes, Dr. Grimmett said yes. Those are four yeses.

How many would disagree? Dr. McMahon, Dr. Young, and Dr. Ho would disagree. No one abstained on that one. That's good enough for me. I'm sure the sponsor would agree with that as well.

Dr. Lepri, did you want anything else on that first issue or can we go on to question No. 2?

DR. LEPRI: That's fine, except are you going to address --

CHAIRPERSON WEISS: Yes. Thank you. Aside from talking about the amount of accommodation, what other performance issues should be considered both generally and for product labeling? This is, I assume, going to be a longer

portion of the discussion.

Product labeling and performance issues. I think you had addressed some of these, Dr. Coleman.

DR. COLEMAN: Some of them.

CHAIRPERSON WEISS: Maybe you could just restate the ones that you have addressed and we could bring them to the panel for discussion.

DR. COLEMAN: I guess in terms of including the less than or equal to plus or minus half diopter change in the MSRE over a year for the stability data of the near acuity and also the intermediate acuity. That's a performance issue.

CHAIRPERSON WEISS: Could you mention the labeling suggestions you had that -- well, I guess that would be -- are you referring to all labeling or basically as it relates to accommodation.

DR. LEPRI: As it relates to accommodation. There is a subsequent question.

CHAIRPERSON WEISS: As relates to accommodation could you give us your recommendations again, Dr. Coleman?

DR. COLEMAN: As it relates to accommodation?

CHAIRPERSON WEISS: Yes, specifically.

DR. COLEMAN: One thing that could be included in the labeling that approximately 50 percent or 57 percent of patients did not need a near add when reading the newspaper and that would relate to information to the surgeon in terms of the use of this lens can subject functionally.

Dr. Bradley, would you want to address that question as well in terms of relating to accommodation or any other labeling?

DR. BRADLEY: I think the labeling is the tricky point. I think the sponsor would like to, and we have already seen from their provisional information they gave us on labeling or description to the patient that this is a lens that provides as the conclusion said, clear vision from distance to near.

Well, quite frankly, it does not and I think that would be very misleading to put that on the labeling. The sponsor would also like to be

able to communicate that this is a lens that achieves accommodation by anterior movement.

I think it's important to be clear that they have never shown that, in fact, this lens moves anterially during near work. I think it would have been great if they had had those data because that would make for a very compelling marketing material it seems to me.

Again, I don't think they have those data so it's hard to make that claim in labeling. Really those are the two main labeling issues that I see.

CHAIRPERSON WEISS: Could you restate those again sort of succinctly or anything that you would suggest?

DR. BRADLEY: Jayne, you've been working with me long enough to know I can't do anything succinctly. I'll try. The claim that this product provides clear vision at near is a misrepresentation of the data and should not be included in labeling.

CHAIRPERSON WEISS: That's fine. I'm

just wondering was that claim made in the patient or the physician labeling? It doesn't really matter.

DR. BRADLEY: I can't recall. It was the summary statement of their presentation this morning so you know it's going to appear somewhere.

DR. COLEMAN: I don't think it was in the physician's labeling. I didn't see it in the patient.

CHAIRPERSON WEISS: We are going to have to address both the physician and the patient later on.

DR. ROSENTHAL: Madam Chairman, Rosenthal.

CHAIRPERSON WEISS: Dr. Rosenthal.

DR. ROSENTHAL: The agency can work with the company on the details of the labeling as long as the panel provides the overview of what the issues are. I think it's clear that representing the results of the study might be better than representing some definitive statement about the performance of the lens. Is that right, Arthur?

DR. BRADLEY: I would concur with that completely and with only one word of warning, that the central issue in this entire discussion is accommodation and we have already established that there is considerable uncertainty about what we are, in fact, talking about. This is not a trivial point. The labeling will be very tricky.

One has to be -- as you are suggesting, the sponsor has to accurately reflect the data, but also be able to communicate these data in a way that is meaningful to both the physician and the patient. It is clear because of this problem of what people mean when they say accommodation. This is going to be a challenge.

CHAIRPERSON WEISS: I would suggest, and I would be interested in the opinions of the panel to include the table where they had actual functional items that patients could do reading, needlework, etc., and include that in the patient as well as the physician labeling. That would bespeak specifics as opposed to generalities. I don't know what the panel thinks.

Glenda Such.

MS. SUCH: Yes. Hi. This goes across both types of labeling. I have a concern. I wanted to mention at the beginning of this that earlier I had heard from the FDA saying that at this time perhaps we should leave the labeling. I think that this panel really needs to be able to discuss labeling issues all the time.

The other issues is about the accommodations and with looking at the clarity issue because of the functional implications of not being able to read newspaper print and that what most people think about if they are going to be able to be told that their images are going to be clear. That is usually their standpoint, not something else. They are not thinking that they are going to have to use any type of spectacles. Even in the labeling that does exist that I have been reading so far, I have been seeing that it talks about all three distances without spectacles so that needs to be, I think, very clear.

CHAIRPERSON WEISS: Thank you.

Dr. Ho.

DR. HO: My guidance -- my recommendations for issues to consider in labeling would be --

CHAIRPERSON WEISS: Actually, I'm just going to clarify this. On question three we'll be specifically talking about all sorts of labeling. For this question we're speaking about labeling that is specifically related to the accommodation.

DR. HO: Okay. From my perspective and from the standpoint of evaluating this new product, I'm thinking about it in terms of visual performance. I think accommodation or mechanisms of accommodation are secondary.

I'm actually not sure that any postmarket study may actually establish what the mechanism is because there are multiple mechanisms of action that may not be relevant for an individual eye that's tested. But for me the acid test is function. I like the idea of including that table.

That speaks to what the patients can understand in terms of near vision, reading the newspaper, intermediate vision, seeing something on a grocery shelf, as a way for them to translate this as a way to assess reducing the need for spectacles.

I think the other issue is you have to view reducing the need for spectacles compared to what implying perfect vision with spectacles is one issue and implying pseudophake with spectacles is another issue. From the standpoint of improvement in our technology, I like the product and I would like to see that spelled out in a way that a patient can understand.

CHAIRPERSON WEISS: Just a couple of points there. One is I think we would all agree it's not the sponsor's job to figure out mechanism, but it is their job to support a claim so if their claim is one of accommodation and they have to show accommodation as far as how that happens, it's up to someone else if they are interested to figure that one out.

DR. HO: Hence, my recommendation to eliminate that word.

CHAIRPERSON WEISS: Accommodation? Well, that's a claim so this is something the panel must determine whether or not we support the claim of accommodation. What the mechanism for that claim is the sponsor does not have to tell us.

The second thing is just because I have asked Dr. Coleman to kindly describe for the labeling issues, I would point out that it sounds like there may be some consensus that the bilateral patient survey activities without spectacles is table 10.5. I think that is something that we will talk about having for the patient as well as the physician booklet.

Dr. Bradley and then Dr. Matoba.

DR. BRADLEY: Is it okay for me to ask the sponsor to step up and answer a question on this particular issue? I need some clarification on that.

CHAIRPERSON WEISS: Yes.

DR. BRADLEY: I have a question about the

survey, by the way.

CHAIRPERSON WEISS: If you could just identify yourself when you come to the podium.

DR. GORDON: Judy Gordon.

DR. BRADLEY: Hi, Judy.

DR. GORDON: I may need to get the data but I'll try to answer.

DR. BRADLEY: I think as I mentioned, 57 percent reported that they could read the newspaper without spectacles. I think we had 30 some could sew.

PARTICIPANT: 38 percent.

DR. BRADLEY: I don't know 38 percent of anybody who sews anymore, so it occurred to me that I was misinterpreting those data.

CHAIRPERSON WEISS: I think it was of the patients who attempted to do that, 38 percent could do that.

DR. BRADLEY: That's what I wanted a clarification on.

DR. GORDON: Patients were allowed to note the response to those items which they

believed were pertinent which is why some of the survey data we presented have varying ends. For example, patients who didn't use a computer simply didn't comment on that.

DR. BRADLEY: Okay. Thank you.

CHAIRPERSON WEISS: Unless you were going to add that to your claims that this would allow you to do these added activities.

DR. GORDON: I don't think that's the plan.

DR. BRADLEY: Thank you.

CHAIRPERSON WEISS: Dr. Matoba.

DR. MATOBA: In the labeling it says almost all patients implanted in both eyes with the CrystaLens had good distance vision after surgery and could see 20/32 or better at distance, i.e., see 20/32 or better at distance. I think that rather than saying almost all, I would prefer to see the percentages. I guess if you put that table in as you suggested, that would help. I think they should point out that the results were not as good if only eye is implanted.

Then later they say the majority of patients could read the paper without glasses. Then the next sentence says almost all study patients could apply makeup, shop, blah, blah, and read a paper without glasses. That second sentence seems to imply that almost all patients could do all of those activities and that's a bit misleading. That's not true. I think they need to be a little bit more accurate and possibly percentages regarding specific tasks.

CHAIRPERSON WEISS: I think Dr. Matoba is looking at attachment to draft brochure for the C&C Vision CrystaLens model and the clinical study results benefits in the last sentence, which I also had a problem with, that almost all the study patients could pass their driver's test.

I wondered could they pass their driver's test before this and does this allow you now to learn how to drive. I think we might have to rescribe that particular -- in fact, maybe we should just eliminate that and just put the amount of people, the actual table 10.5. Would you agree

with that?

DR. MATOBA: Yes.

CHAIRPERSON WEISS: I see agreement, Dr. Ho, Dr. Matoba. Dr. Bradley is raising his hand. Yes.

DR. BRADLEY: A lot of that table appears very -- provides a very optimistic view of the product. We get these very high percentages. The whole point -- the novel point of this product is that it provides good near vision. There are only a couple of items in there that really address the issue of near work.

In a long table like that, there at the bottom by the way, they could easily be lost after you've seen all these 95 percents. I think if the table is going to go in there, I think some sort of emphasis of the near work survey questions should be made.

CHAIRPERSON WEISS: Do you have this?

DR. BRADLEY: I do.

CHAIRPERSON WEISS: I'll just read it out and as long as we are addressing this issue, maybe

we can finish up with this point and then break for lunch.

The sentence that Dr. Matoba was referring to, and I'm also speaking about, reads, "Almost all of the study patients could pass their driver's test, could see their computer, shop, or apply their makeup, and could read a newspaper without glasses or contact lenses."

I would ask if anyone from the panel could wordsmith this particular sentence which could convey more accurately that there was improved near vision but that if you were doing something that was extremely up close, you probably would need glasses.

Dr. Bradley.

DR. BRADLEY: Yeah, I think I would follow Ralph's suggestion that we don't wordsmith it but we let the FDA realize that sentence if it is going to appear in this product description, it must accurately represent the data. My personal add is to ensure that the near work data be emphasized because that is the novel claim of this

particular product.

CHAIRPERSON WEISS: So would it be satisfactory to the agency if the panel then just suggested that the physician and the patient labeling indicate there was improved near vision with this lens but certain tasks still would require some glasses in a percentage of patients?

DR. ROSENTHAL: If that is what the panel would like to recommend.

CHAIRPERSON WEISS: I'll put that to the panel. Is that what the panel would like to recommend?

ALL: Yes.

CHAIRPERSON WEISS: So I hear actual consensus on this one which means it is probably time for us to break. I'm going to let the panel know that we are having a meeting in the hotel's private dining room so I would like everyone from the panel to meet there. We are going to be breaking one hour for lunch so if everyone could be back here promptly.

EXECUTIVE SECRETARY THORNTON: Yes. This

is not anything to do with the PMA that we are discussing now. This is a presentation that FDA has planned for you on a totally different matter.

CHAIRPERSON WEISS: So we are adjourned for lunch.

(Whereupon, at 11:55 a.m. the meeting was adjourned for lunch to reconvene at 1:00 p.m.)

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

1:14 p.m.

CHAIRPERSON WEISS: I would ask all the

panel members to take their seat. We are going to begin the afternoon session. Sally Thornton has an announcement.

EXECUTIVE SECRETARY THORNTON: Something to add to the updates for the Diagnostic and Surgical Devices Branch that just came in hot off the press.

On May 23, 2003, we approved P930016 Supplement 16 for the Visics Star S4 Wavescan indicated for wavefront guided Lasik for the reduction or elimination of myopic astigmatism up to minus six diopters MRSE with cylinder between 0.00 diopters and minus three diopters at the spectacle plane. That's the end of the announcement. Thank you.

CHAIRPERSON WEISS: I would ask the FDA if they could put their questions back on the screen so the panel could proceed through those questions again.

I think we finished off with the first question unless anyone has any other comments. Seeing no comments, we'll go on to the second

question.

2. Do you believe that the sponsor has demonstrated the stability of the hinge, and therefore the stability of the accommodative refractive effect?

Dr. Coleman.

DR. COLEMAN: Well, in my review I felt that the long-term stability evidence had not been established beyond at least 10 years if you believe in flexibility of the lens. And then in terms of more than one year in terms of the clinical data that they provided.

CHAIRPERSON WEISS: Do you want to say 10 years?

DR. COLEMAN: I think we had suggested --

CHAIRPERSON WEISS: Do you just want to say long-term stability has not been established?

DR. COLEMAN: Yeah, I think that was what we had kind of -- because also that came from Dr. Bradley's review also was a recommendation in terms of having it on the labeling indicating that long-term stability had not yet been established.

CHAIRPERSON WEISS: Do you think it would be important to differentiate between the stability of the hinge and the stability of the accommodative refractive effect to indicate that the long-term stability of neither of those issues had been established, or would you like to lump them?

DR. COLEMAN: I think for the stability of the hinge they have shown some stability of the hinge up to a million cycles whatever that applies to clinically in terms of movement of the lens. In terms of the accommodative ability clinically based, that was only up through the one-year clinical trials so you could divide them up.

CHAIRPERSON WEISS: So you would like to basically add something and, if I may speak for you and if I am incorrectly representing you, please let me know.

DR. COLEMAN: I will.

CHAIRPERSON WEISS: You would like to add something saying that long-term stability has not been established for the hinge or the accommodative refractive effect. Any other comments on this

issue?

Dr. Bradley. We wait with baited breath.

DR. BRADLEY: I was curious about what we might anticipate if the lens hinge failed or started to fail. It seemed to me that the hinge might become weaker and potentially get more accommodation out if the hinge is providing any resistance at the time it goes in. I'm not sure a partial failure is a bad thing in this particular device.

It might actually enhance its effectiveness. Presumably what we are looking for is a major mechanical failure of the hinge in which the lens becomes unhinged and then presumably it's then dangling somewhere inside the eye and of little optical value.

I was just going to say that in terms of the catastrophic event it seems pretty clear that a million of these movements forward and backwards seems to provide no noticeable damage to the lens.

As I said in my review, because we haven't seen actual evidence that the lens is

moving during near and distance work, then we are not sure whether a million cycles is adequate or inadequate at this point. That's the problem.

CHAIRPERSON WEISS: I would also ask the panel if they think it would be possible, say, if there was a hinge failure at a certain number of cycles might one portion of the hinge be damaged earlier than the other and the lens now go into an oblige angle or rub against the iris. Personally I don't think we have any information on this but I would ask the panel for their comments on that particular issue.

DR. BRADLEY: I think in terms of -- this is Arthur Bradley. In terms of labeling, I think, again, state the data. A million movements. No visible damage to the hinge. One year after implantation seems to work as well as it did just after it was implanted. At this point that's all we have.

DR. COLEMAN: So we have no information on what happens if one of the hinges doesn't work and the other one does so you have an oblique.

CHAIRPERSON WEISS: I think we will still go back to what you were suggesting, long-term stability of the hinge has not been established. Long-term stability of accommodation has not been established.

Dr. Rosenthal.

DR. ROSENTHAL: Rosenthal. Do you think it might be reasonable -- what do you think would be reasonable to include in labeling about the potential for one hinge? Do you think it should be mentioned or do you think it should not be mentioned at all?

CHAIRPERSON WEISS: Are you addressing this to the panel or to me?

DR. ROSENTHAL: To the panel. As a remote possibility.

DR. COLEMAN: I think it would be important to mention it as a remote possibility so that the surgeons can mention it to the patient that this might potentially happen. Although the effect on the patient's acuity with an oblique situated lens is not established.

CHAIRPERSON WEISS: Dr. Matoba and then Dr. Bradley.

DR. MATOBA: Actually, I wouldn't mention it because we have no information that would ever happen so it is so theoretical that I would not mention it.

CHAIRPERSON WEISS: Dr. Bradley.

DR. BRADLEY: I think panel speculations should not be part of the labeling.

CHAIRPERSON WEISS: Dr. Grimmett.

DR. GRIMMETT: Dr. Grimmett. I similarly would not mention it speculating on what might happen when we have no evidence that it will happen is not proven.

CHAIRPERSON WEISS: Dr. Matoba.

DR. MATOBA: And also I would not say that after million excursions there was no noticeable damage because I think that is misleading. They may think, "Oh, it's way beyond my lifetime," but we don't know that. It could be a year or less. I would just say long-term stability has not been demonstrated.

CHAIRPERSON WEISS: Dr. Bradley and then Dr. Young.

DR. BRADLEY: I will reiterate how easy it would have been to answer this question if the sponsor had provided us with dynamic measurements of refraction during normal distance and near fixation because we would have seen, in fact.

If the lens was oscillating, we can estimate -- make some sort of estimates about how many times this lens is going to flex over a certain period of time. At this point we really don't know because we have no data.

CHAIRPERSON WEISS: Since you introduced that subject, I will take rest from this question a little bit and ask whether you then would want some ancillary studies or you do not feel they are necessary for approval of this?

DR. BRADLEY: It seems to me the sponsor could have much more compelling arguments in favor of this product to be included in the physician's and the patient's information if they did a study showing that the lens actually moved as designed to

move. That is from their perspective.

From our perspective as long as the claims do not claim how they think the lens works but the fact that they don't have actual evidence that it works that way, I think they are fine. I don't think that affects approval. It just affects what claims they can make.

CHAIRPERSON WEISS: But you are still comfortable with the claim of accommodation of one diopter without that extra data?

DR. BRADLEY: Yes.

CHAIRPERSON WEISS: Fine.

Dr. Young.

DR. YOUNG: I was just going to mention that I concur with not mentioning hinged dislocation or optic dislodgment or oblique angle. The only way we can really study that is if we have histopathologic studies of actual hinge integrity. That's obviously not going to be the case for this.

CHAIRPERSON WEISS: Would anyone want to put in the labeling regarding long-term stability

that the lens has only been studied for a period of time that it's been studied?

DR. COLEMAN: What do you mean?

DR. SLADE: What was that question again?

CHAIRPERSON WEISS: For a year or two.

DR. HO: Allen Ho. I would just say that we can say very little. I mean, what's of relevance is the visual function overtime. I think a claim that stability of visual function to the endpoint that they showed is reasonable but beyond that I would say it's unknown and that's what's relevant.

CHAIRPERSON WEISS: So are we still at accommodative stability and hinge, those two words?

DR. HO: I have no problem with omitting hinge. I don't think people care about hinge. I think they care about how they see.

CHAIRPERSON WEISS: I personally would care about the hinge only because I'm concerned if the lens did dislocate not only would it affect vision but it could cause iritis or something like that. I would prefer to keep that in there. It

might not have relevance but I would prefer to keep it in there.

Dr. McMahon.

DR. McMAHON: Tim McMahon. The data suggest that visual acuity or visual function is stable at one year. I don't think we can actually say much more beyond that which is sort of echoing what Dr. Ho is saying.

I don't think that we can say this has anything to do with stability of the hinge because we don't really know whether the hinge is moving at all. We have some suspect or suggestive information might be moving a little bit, but at the same time one can make the argument it's really not moving hardly at all anyway.

Arthur made the suggestion that we not speculate in terms of various different functions of this lens and I agree with that. I think the information should be limited to what the data support and that is that visually acuity is stable. There are different differences at a one-year period.

CHAIRPERSON WEISS: Just in terms of the last comment you just made and the patient labeling, there is something that states CrystaLens moves backwards and forwards. Is that something that you would want taken out of there? How does the panel feel about that? I don't want to go sentence by sentence but just because you brought that up.

Dr. McMahon.

DR. McMAHON: There was going to be a point that I suggested that be removed from the labeling.

CHAIRPERSON WEISS: Good time to make that point.

Dr. Bradley.

DR. BRADLEY: Again, perhaps for clarification, it might be adequate -- acceptable to say that the lens is designed to move forwards and backwards and, in fact, it can do this. Sort of a bit of wordsmithing there but it never shown it doing this in the circumstances in which it was intended to be used.

That is a shortcoming that the sponsor has to deal with. If I could put myself in the sponsor's shoes, I would rush out and do that right away because I would like to make that claim, but without the data I'm not sure they can make that claim at all.

CHAIRPERSON WEISS: Forgive me, Ralph, because I know you don't want to go through sentence by sentence but there is --

DR. ROSENTHAL: No, that's fine to pick up areas that you want to discuss.

CHAIRPERSON WEISS: In the patient labeling it says as stamped, "The CrystaLens moves backwards and forwards inside the eye at the brain's command to focus the lens to provide distance, intermediate, and near vision and reduce your need for glasses or contact lenses after surgery." What does the panel think about that sentence? Are you comfortable with that sentence?

Dr. Bradley.

DR. BRADLEY: I guess I'm not so

comfortable with it. I think -- I'm just going to repeat myself.

CHAIRPERSON WEISS: Rather than repeating yourself can you give me -- not that I mind listening to your repetitions but can you give me an alternative or suggestion for the labeling that would answer what your concerns are?

DR. BRADLEY: Certainly a recommendation would be -- recommendation to the FDA would be to require the sponsor to actually show that is true prior to putting that in the labeling.

CHAIRPERSON WEISS: Fine. So just eliminate it from the labeling. That's easy. Any other thoughts on that particular issue?

DR. McMAHON: This is Tim McMahon again. I would concur.

CHAIRPERSON WEISS: Dr. McMahon concurs. Any other discussion?

Dr. Ho.

DR. HO: Yeah, I'll wordsmith it. I would say that the CrystaLens with respect to that attachment sentence that you're speaking to, the

CrystaLens simply reduces your need for glasses or contact lenses for intermediate and near vision after surgery.

CHAIRPERSON WEISS: I think basically you are agreeing let's take out -- suggest that mechanism of moving backward and forward be removed. I think this would then lead us into question No. 3 unless there are any other comments on question No. 2.

Question No. 3. Does the panel recommend any other modifications to the proposed physician or patient labeling?

We have at this point discussed about the issues about the accommodation, the issues about the movement of the lens and the stability of the hinge and the stability of the accommodative refractive effect. I would add personally that perhaps we should indicate that the visual results may not be as good if only one eye undergoes the implantation. I see some agreement by Dr. Ho and Dr. Young.

Dr. Matoba, you have a comment?

DR. MATOBA: I think we mentioned that under when we previously discussed labeling and I agree.

CHAIRPERSON WEISS: What other labeling issues -- actually, this would be the point, Dr. Coleman, if there are other labeling issues, you could bring those up, and we'll go to Dr. Matoba and Dr. Young and then Dr. Grimmett in that order.

Dr. Coleman.

DR. COLEMAN: One was to aim to plano instead of minus half sphere. The other was to include the information on the stability of near acuity and intermediate acuity and distance acuity in the physician labeling.

The other one was a warning precaution, the effect and performance of the lens is unknown. Another is to include Table 10.3 from the patient survey on the frequency that subjects wore the glasses.

CHAIRPERSON WEISS: Is that Table 10.5?

DR. COLEMAN: 10.3. 10.5 has already been recommended.

CHAIRPERSON WEISS: So we'll have 10.3 and 10.5.

DR. COLEMAN: That's page 150 of 195. It is, "How often do you wear spectacles during waking hours." "I do not wear spectacles" in 26 percent. "I wear spectacles almost none of the time" in about 48 percent. That table.

CHAIRPERSON WEISS: Okay. 10.3 and 10.5.

DR. COLEMAN: Mention as precaution the range of the axial lengths and lens powers that were used in the study. Mention on page 2 of the physician labeling that atropine should be given immediately post-operating and post-operative day one. Include under adverse events the possible increased rate of CME associated with sulcus-bag placement of haptics. And then other issues that came up for physician labeling. Do you want those?

CHAIRPERSON WEISS: Yes, please. As we go around, just give me every labeling concern that you have.

DR. COLEMAN: These are from everybody. Mention that the accommodative amplitude appears to

be about one diopter or less. Mention that the mechanism of action is hypothetical, that it's a hypothetical mechanism of action that hasn't been proven yet in terms of the claims in the studies that have been done.

Then we also had recommended to mention in both the physician and patient labeling table 10.5 and emphasizing that 57 percent of patients do not need a near add to read the newspaper meaning that 43 percent do need to use a near add. Another suggestion -- I did not see clear vision mentioned in any of the physician or patient labeling but make sure that is not --

CHAIRPERSON WEISS: Actually, the sponsor mentioned to me in the break that was only included in the presentation of the sponsor. It was not included in any of the written materials so we can actually take that out of the equation.

DR. COLEMAN: Okay. In addition, include Table 10.5 in both the physician and patient labeling and make sure that you emphasize the near work on Table 10.5.

CHAIRPERSON WEISS: So perhaps another line saying, "For certain near visual tasks or for very close work many patients do require glasses."

DR. COLEMAN: Correct. And to mention in the patient labeling the percentages of those individuals that do need glasses for near work so not just focusing just on the newspaper information.

Then for the patient labeling we wanted to delete the clinical study results, the last sentence. We had mentioned that, in attachment 2.

CHAIRPERSON WEISS: "Almost all the study patients could pass their driver's test." The sentence that begins with that.

DR. COLEMAN: Right. And then just the ones that we just mentioned about the claims that the lens moves back and forward should be deleted stating that the lens can be designed to do this as Dr. Bradley suggested.

The beginning of the statement, "At the brain's command the lens moves back and forwards," as was just wordsmithed by Dr. Ho. Then also

including in both the patient and physician labeling that the surgical results may not be as good if only one eye is done versus two eyes.

CHAIRPERSON WEISS: Thank you very much for that list.

Dr. Matoba.

DR. MATOBA: We should add that the lens has not been studied in patients younger than 15. Are we going to discuss each of these points, these suggestions?

CHAIRPERSON WEISS: Yes. This is the time to do it so if there is anything that is suggested that you have a comment on, agree or disagree, please let us know.

DR. MATOBA: Okay. I would disagree with the recommendation to go for plano rather than minus half because I don't know about your department but we are not that accurate and you don't want to overshoot and end up with a hyperopic patient. For the first eye I wouldn't change that recommendation from minus .5. I would keep it at that.

CHAIRPERSON WEISS: Dr. Bradley, did you have a comment or are we going to go on?

DR. BRADLEY: I do have a comment but I'm waiting for the list.

CHAIRPERSON WEISS: Dr. McMahon and then Dr. Grimmett and then Dr. Bradley.

DR. McMAHON: I concur with Dr. Matoba's discussion about leaving the surgical recommendations as is at minus half for the first eye. If nothing else, I think that potentiates the advantages or the benefit of this lens as is.

I want to raise a little different issue and that has to do with the age of the patient. If for the moment, and this hasn't been proven to my satisfaction, that this lens does move, we have now a revolutionary devices that is actively doing something inside the eye rather than just passively sitting there.

We have a trend, though not statistically significant, in their one-year data suggesting a higher degree of uveitis and CME in these patients. I suspect that is not going to be a completely

irrelevant issue.

One of the questions I want to raise for the panel is whether we should initially limit the age at which this procedure is done. Right now the sponsor wants it at 18. I would actually postulate that maybe this shouldn't be done on anybody under age 60 or 65 until some intermediate term record exist.

Now, on the other hand, if the sponsor had provided information that says, indeed, it doesn't move, that the near vision effects are from some other reason, it makes my particular suggestion moot. As Dr. Bradley has pointed out so eloquently, this particular issue hinges in all sorts of orders.

CHAIRPERSON WEISS: The sponsor is printing the numbers now to figure out which one would be better.

Dr. Young and then Dr. Grimmett and then we'll go back to Dr. Bradley.

DR. YOUNG: I had discussed earlier the issue of the YAG capsulotomy and whether or not

that has some effect on movement of the lens and had suggested a warning or precaution that the effect on accommodative performance of YAG plus your capsulotomy prior to 12 weeks is unknown.

The other comment was that most practices use a non-immersion method to determine axial length. I thought a comment that immersion method may be preferable for IOL calculation parameters for this device also be added as a comment for labeling.

CHAIRPERSON WEISS: I would think that would be in there already. Could I just ask the sponsor? I would assume you already have that in there that you want immersion method to be done in physician labeling.

DR. GORDON: I'm not sure but we certainly have the data. We'll confirm and take a look but we certainly have the data to support that and it was presented for that reason today so we are seeking input from the panel.

CHAIRPERSON WEISS: We could add that and if it's in there, then it will just be removed by

agency. That's fine.

Dr. Grimmett.

DR. GRIMMETT: Michael Grimmett. The age comment, I'll just add one thing. Dr. Matoba and Dr. McMahon already made the comment. In the draft labeling in Vol. 1 on page 3 it does say, "Implantation of the CrystaLens should not be performed in patients under 18 years of age."

That's seemingly implies that over 18 is A okay. I think that somehow needs to be revised that this study only included patients 50 years of age or older because that particular statement implies something different. I would definitely make sure that statement is revised.

On page 9 of 18 in the draft labeling the lens optic is listed, diopter power 10 to 30. To the best of my knowledge the study used between 16.5 and 27.5. This may be standard practice.

The FDA expands the limit of the lens range to when they can produce more lenses. Clearly this study did not look at 10 to 30. Again, I was looking at the 16.5 to 27.5, I think

from page 117, tab 8.5. I think that needs to be revised.

I'm going to make one "get up on the soapbox" comment and get to a labeling issue. A major concern that I have with this lens as just a clinician is the small optic size. A 4.5 millimeter optic is concerning to me.

I think that senile pupillary miosis may be a protective factor here for the older age range. I would have extreme concerns if this lens were put in a younger subset. If their in dim illumination meets out the conditions they had pupillary dilation to the extent that the normal physiologic range can occur, I think they probably would have symptoms.

Additionally, a second point regarding a small lens optic. I know that the retinal surgeons will not appreciate doing peripheral retinal examines through a 4.5 millimeter optic lens or trying to laser a peripheral retinal hole for lattice, or even in a diabetic patient looking at the peripheral retina.

I think that would be difficult. I hope that sound clinical judgment would prevail, that small lens optics are considered in patients with retinal pathology. I do understand that the indications say don't implant it in someone with retinal pathology but I think that's an issue.

Lens centration on this lens with a 4.5 millimeter optic is critical. Dr. Slade's comments that the lens does center exceptionally well is reassuring, but I think that any decentration on a lens this small is a major factor.

This will lead me into what I want in the labeling. Table 10.7 on page 153 of 195, under tab 10, Patient Survey, lists difficulty for nighttime activities. I think with a lens optic this small, I think that is a relevant table and I would want to see that in the labeling.

If you look at patients who had any symptom, that is, either glare flair, difficulty driving at night, or halos at any range, mild, moderate, or severe, a full 52 percent of patients had some symptom. If you look at just moderate or

severe of any symptom, 27 percent had some symptom. I think that is a relevant table in a lens with a 4.5 millimeter optic. Especially if you have a patient with a large pupil.

I think that somehow in the labeling there has to be mention of that fact either simply by including that table or stating the issue of the effective IOL optic diameter of the pupillary plane wherever this lens happens to sit as we discussed earlier. I think that is an issue that does need to be made in the labeling because as a clinician that's what would concern me.

CHAIRPERSON WEISS: Could I just ask you to sort of list the various things that you would suggest as conditions?

DR. GRIMMETT: Sure. I included the ones on the labeling about 18 years of age or older. That was number one. That was on page 3 of 18. No. 2, I wanted the lens power range amended. It's listed 10 to 30 but I somehow want to clear that the study only looked at 16.5 to 27.5. Of course, the FDA will use prior precedent to expand the

ranges they ordinarily do.

Then No. 3, at a minimum I would like to include Table 10.7 on page 153 of 195 under Tab 10 listing the difficulty for night activities. I would like to hear other comments from the panel regarding comment about a 4.5 millimeter optic whether that type of comment in mydriasis needs to be added. I would like to hear other opinion on that.

CHAIRPERSON WEISS: We're going to have Dr. Bradley and then Dr. Matoba.

DR. BRADLEY: Two main issues regarding labeling. One comes back to the point that Mike Grimmett has just been making. The sponsor has done an analysis indicating that a 4.5 millimeter optic is adequate.

I think the sponsor is probably correct under most circumstances in the age group which they have used for this study. That is, 50 years and older. I think Mike Grimmett raises an extremely important point that in younger eyes where pupil size can be considerably larger than

4.5 and routinely can be 7 millimeters or greater.

These young eyes installed with this lens will effectively have less than half the area of their pupil covered by this lens. Effectively they will be aphakic for half of the light and phakic for the other half of the light. We all pretty much understand the consequences of that.

I think all the lawsuits that are now floating around with patients who are treated with refractive surgery with a small treatment zone and their pupils were larger than their treatment zone, we all kind of understand the consequences of this mistake.

We all kind of understand the consequences of this mistake. They are quite profound within the profession and I think that it would be important labeling for the clinician to understand that the size of this optic will produce problems if you fit it to a patient with pupils larger than 4.5 millimeters.

That pretty much includes every young

adult. The notion of fitting down to age 18 I think would be disastrous for the patient and for the surgeon who fitted it. I think Mike's point is extremely well taken and one that should be clearly articulated in the physician labeling.

I would discourage the sponsor from seeking approval to have this lens installed into eyes younger than 50 years of age. In fact, I would recommend that prior to installing the lens some examination of the chronic pupil size is done. Again for the same reasons that we've had had problems with refractive surgery. We do not want pupil sizes bigger than the optical zone. This is bad news for everybody. That is the first point. That is physician labeling.

Patient labeling. My concern here is one that I feel with this barrage of data, indirect evidence, confusion over definitions, that patients may not really understand what they are getting into with this lens. I'm wondering if there is a way to describe this product in a way that would be clear to a patient and, therefore, would be ideal

for product claims in the patient description.

A thought that comes to mind is to point out that this lens may give one diopter. I'm not sure that makes sense to a patient right away from, anyway, one diopter of extra power and, therefore, will give you clear distance and intermediate vision but it does not provide clear near vision.

You may under some circumstances, for example, reading the newspaper, require a reading add. To help the product is to clarify that this is better than you would get with a standard nonmoving IOL. The important point is that the lens seems to provide clear vision at distance and intermediate. It is at near that it doesn't provide clear vision but the vision seems okay at near. Somehow to communicate that to the patient so they know what they're getting into. With this lens they will be able to see fine at distance.

They will be able to see fine when they are watching TV or putting on their makeup or whatever it happens to be. But when they sit down

to read the newspaper they may need an add. Somehow to communicate that so that the patient knows exactly what they are getting into I think would be valuable.

CHAIRPERSON WEISS: We are going to go on to Dr. Matoba in a moment but I just want to comment on two things. As a refractive surgeon I would say the role of the pupil size with the symptoms is still not clear and elucidated. But with this lens you still may want this particular caveat.

The other thing is I would personally prefer to stay away from the word clear. Why don't we don't talk about improved or functional so that you don't need glasses. And maybe for near vision the percentage of people will need glasses, where for distance and intermediate the vast majority of people have excellent vision without glasses. I'll leave it to Dr. Matoba to work that out for us.

DR. MATOBA: Well, my comment is that I agree with Dr. Grimmett's comments. That was the thrust of my questions I asked before lunch

regarding pupil size relative to patient satisfaction and symptoms and also the contrast sensitivity study that they did.

The sponsor said they had not stratified by pupil size patients complaints and their function. I think if that data was available it would be useful to see that. Then it might help us to set some guidelines in terms of labeling for what pupil size we would not recommend that the eye will be implanted.

Also the contrast in sensitivity of these sponsors I think said that they had stratified that data by pupil size but I don't see it in this protocol. I think they looked at the contrast sensitivity under mesopic and photopic conditions but under the mesopic conditions the average pupil size was 4.2.

It's pretty small. The range was 2 to 7 so if they can go back and look at how well the people with 7 millimeter pupils functioned versus the two, that might be useful information.

CHAIRPERSON WEISS: Just so we can

summarize somewhat, in terms of the issues about pupil, Dr. Matoba, you would prefer that the sponsor come back and actually stratify the pupil size versus the results or the contrast sensitivity to give some gauge if that had an impact?

DR. MATOBA: Or at a minimum patient satisfaction because, I mean, I share Dr. Grimmett's concerns that 4.5 is a size that is of some concern. There are some theoretical problems with that.

CHAIRPERSON WEISS: Okay. So you would like the sponsor to come back and give the agency some information about pupil size and patient satisfaction.

Dr. Grimmett, would you like to go beyond that as far as the pupil size concerns or that would satisfy the issues?

DR. GRIMMETT: Well, I would prefer that a statement is made in the labeling just stating that the lens optic size is 4.5 millimeters and mesopic large pupil sizes may induce visual aberration. Something of that nature just to state

what we're all getting at. We know that to be true both from our clinical practices and from literature.

I think the Table 10.7 that list almost a third of patients at moderate or severe, any symptom at night is pointing to the fact that there are some visual aberrations going on here even in this subset age 50 and older.

My concern comes to knowing other things obviously about the market. The FDA nor the manufacturers has a duty, nor is obligated to handle off-label uses, but we know from the array of lens that in the market place surgeons offer off-label uses of clear lens extraction for presbyopia.

I think for this particular product with a 4.5 millimeter optic if that PreLEX presbyopia lens exchange surgery was advocated, I think that we need to preemptively put in the labeling alerting the physician to the fact that this is a 4.5 millimeter lens otic and has some concerns regarding dim illumination mydriasis. That's why I

would favor putting it in.

CHAIRPERSON WEISS: Specifically for that concern would you want to say, "This is the size of the optic. We don't know the effects if you are younger and you have a large pupil and consequently this is not recommended for PreLEX?" Do you want to go that specific?

DR. GRIMMETT: No, I wouldn't say that. I think it is a 4.5 millimeter optic. The manufacturer has already told us that this particular lens sits however many millimeters back from the corneal plane making the effective optical zone that the pupillary plane equals X.

They threw out a number of 5.4 but that was for a lens that sat further posterior so do the calculation for wherever this lens happens to sit.

Given those two facts, then I would make the next statement, that pupil sizes larger than this may induce visual aberrations, e.g., mydriasis and dim illumination.

CHAIRPERSON WEISS: But then aren't we

speculating just like we were for the oblique lens?

DR. GRIMMETT: Arthur?

CHAIRPERSON WEISS: I take that as a yes.

DR. BRADLEY: Mike's deferring to me and presumably he knows I'm good at speculating. I think we don't need to speculate at all. I think it's very simple optics. I mean, if you have a small enough optical zone and the pupil size is large enough, light will get to the retina without passing through the optics.

We are all aware, I think, right now that if a laser came to the panel right now that was designed to correct small amounts of myopia or intermediate levels of myopia with an optical zone considerably smaller than the anticipated pupil size, we wouldn't approve such a device.

CHAIRPERSON WEISS: What's the statement you want to put in there? Cut to the chase.

DR. BRADLEY: Cut to the chase.

CHAIRPERSON WEISS: Does anyone have a line that they would suggest to sort of summarize the concerns expressed here?

Dr. Coleman.

DR. COLEMAN: Maybe you could put it under the precautions that data for subjects younger than 50 years of age or with pupils greater than 4.5 millimeters unless this is provided to the FDA is not available and so the effect in these individuals of the small optical zone is of concern or is unknown.

DR. GRIMMETT: Mike Grimmett. I think Alice said the range actually was something up to 7 millimeters, right? So there were some patients that had larger pupil size in all fairness. It's just that it wasn't stratified.

We are using -- I think the basis here is we're not using evidence from their study to say what happens in patients with large pupil sizes with a 4.5 millimeter optic. We simply don't have those data.

CHAIRPERSON WEISS: I think we'll get back to what Dr. Matoba suggested originally is this is a concern and if the sponsor gave this information to the agency, then the agency could

determine what to do with that information as far as additional labeling. I see Dr. Rosenthal agreeing so I think that is probably --

DR. GRIMMETT: I think the FDA understands the intent of our concern regarding dim illumination mydriasis.

CHAIRPERSON WEISS: What about the concern of Dr. McMahon's about the increased uveitis and CME rate? Do panel members want to include that in labeling and, if so, how?

Dr. Coleman.

DR. COLEMAN: I think that's in the labeling in terms of they gave the rates of the uveitis and CME.

CHAIRPERSON WEISS: Do you want to say anything additional about it or the table is fine?

DR. COLEMAN: There is something written. In addition, also so you know, on the precautions on page 2 of 18 the immersion biometry is recommended for axial length so that is there.

CHAIRPERSON WEISS: While you are looking that up --

DR. McMAHON: Dr. Weiss, can I address that question?

CHAIRPERSON WEISS: Yes, Dr. McMahon.

DR. McMAHON: The purpose of raising those and, again, sort of trying to adhere to the issue of limiting speculation was a relative concern of whether we should address the age of the patient, therefore, the exposure of the eye to this lens until greater information is made. The data that they have is the data they have.

There is a trend but maybe that is just a statistical fluctuation. One would expect in a moving object inside the eye a higher incidence of these sorts of things. The reason I mention those two isn't to specifically point them out in the labeling. They are already identified. The issue is should we ask the sponsor to limit implantation of this lens to an older age group until such time there is adequate evidence to go to a younger age group.

CHAIRPERSON WEISS: Dr. Grimmett, do you have an opinion on that?

DR. GRIMMETT: I certainly would make a statement that the lens is only studied in age 50 or older and that it is not recommended for less than age 50 for the reasons we've stated. Dr. McMahon's concern about there's no data and the ongoing iritis or the CME issue. The issue that we previously discussed regarding young patient mydriasis, I think that is a second strong reason not to recommend under the age of 50.

CHAIRPERSON WEISS: You could have a blanket statement saying use of this lens in younger patients with larger pupils. Or you can just say simply that it hasn't been studied, just as we said, in anyone younger than 50.

DR. GRIMMETT: The lens was not studied in patients younger than 50 and use of the lens in patients younger than 50 is not recommended. I would even go further. Not to just say it wasn't studied. It's not recommended from this panel. Is anyone here recommending that it is used under age 50? Okay. It's not recommended.

CHAIRPERSON WEISS: I would differ with

that. I would personally prefer to say we don't know rather than whether we recommend it or not. We don't have any data to recommend it or not. I think it would be unfair to say we don't recommend it without any information.

DR. GRIMMETT: Well, when they come up with data the labeling will be changed. The FDA is reasonable and they will look at new data for under age 50 and if it supports safety and effectiveness under that age group, then that statement will be removed.

CHAIRPERSON WEISS: How does everyone feel about this discussion?

Dr. Bradley.

DR. BRADLEY: I think Jayne's suggestion that we simply don't comment on whether we think it's a bad idea to fit this with younger eyes I think is wrong. Although we don't have any data, we have clear theory which tells us that if the pupil is too large, light will get past the optical zone and then you will have a tremendous amount of blurred light on the retina.

It's not speculation in this particular case. It must be true. I think putting a warning in there to alert the physician to this is reasonable. I agree with Mike.

CHAIRPERSON WEISS: Do we have that data though? Isn't that what Dr. Matoba is requesting to seek patient satisfaction with pupil size?

DR. BRADLEY: Suspicion is in this age group. You will find very few patients who have pupil sizes the same size that we would expect routinely in this 18 to 30 age group.

CHAIRPERSON WEISS: So should we be waiting for extra data before you make that statement as opposed to making that statement without the data? I'm throwing this out.

Dr. Matoba.

DR. MATOBA: We don't know that. I think the average pupil size is small but the range, for example, as I said for the contrast sensitivity for the mesopic conditions the average pupil size was 4.2 but the range was 2 to 7 so there may be a number of patients that you can look at to answer

this question.

DR. BRADLEY: I think you have a couple of patients and that does not allow you to answer the question. I mean, basically you need a large sample here and you are only going to get a few people who have a pupil size that large in this age group where it is routine. My students you put them in a room and they all have pupils of 7 millimeters or more.

CHAIRPERSON WEISS: Dr. Coleman, do you have a comment on this?

DR. COLEMAN: I think we need the data so I agree with Dr. Matoba.

CHAIRPERSON WEISS: So actually I would sort of like to address this point as well. It sounds like there is a little bit of a conflict. I would like a show of hands in terms of panel members who would support putting an item in there saying that specifically this is not recommended for patients below a certain age.

The alternative for the other panel members who have a concern but don't want to voice

that opinion would be to get the additional data and then make a conclusion on that basis. In any case, let's just state it as I did initially.

Can you vote in the affirmative if you would like to put something in here saying that this is specifically not recommended for younger patients and we could determine whatever age you want to put. That's affirmative by Dr. Grimmett, Dr. Young, Dr. McMahon, and Dr. Bradley. How many of you would vote against that? We have affirmative by Dr. Coleman, Dr. Ho, and Dr. Matoba, and Dr. Weiss who has no vote in this process. We will move on from there.

MR. McCARLEY: Excuse me. I have a question.

CHAIRPERSON WEISS: Yes, Mr. McCarley.

MR. McCARLEY: Rick McCarley. Just a question to the FDA. Are there any lenses, intraocular lenses for cataract surgery that are 4.5 right now that are approved? Is there one? So, in fact, this is the first --

DR. ROSENTHAL: Rosenthal. The answer is

no.

MR. McCARLEY: Okay. So this, in fact, would be the first one. But just for consistency sake, wouldn't this apply to labeling for all intraocular lenses if you are saying an intraocular lens should never be placed into a patient whose pupil size is larger than the optic? Why would you restrict that to this lens? Why wouldn't you put that across all lenses?

CHAIRPERSON WEISS: Dr. Bradley.

DR. BRADLEY: I think the point you make is a good one but we obviously are just considering this lens. Other lenses have been dealt with perhaps differently but we are dealing with this particular lens and we have a concern about this lens.

It seems that the precedent, fortunately, is not there but there is a 4.5 optic zone out there already approved. If that were the case, then I think we would be challenged doubly here. But the fact is that is not the case. I think this is a new type of small optic zone that warrants our

careful consideration of this pupil size issue.

MR. McCARLEY: But it seems to set a precedent that you shouldn't have any patient regardless of their age. I mean, this is an age cutoff issue we are dealing with here. Age cutoff based upon pupil size, I'm not sure those are --

CHAIRPERSON WEISS: We can try to make the labeling for each specific PMA as excellent as we can make it and that's our goal. We actually had a similar issue last meeting and I think we had a similar discussion last meeting about having higher standards for one PMA than another. We would like to have standards for every PMA so if that is what the panel wants to do, that's what the panel wants to do.

Dr. Rosenthal, did you have a comment on that? No comment. Then Dr. Matoba and then Dr. Ho.

DR. HO: Allen Ho. We have no evidence to recommend for or against this lens based on that age. Therefore, I have no evidence, no basis to make a statement.

CHAIRPERSON WEISS: Dr. Matoba.

DR. MATOBA: Plus the concern is regarding pupil size so what if you are 25 but you have a very small pupil and you can't get that IOL. That is why I don't agree with recommendation to prohibit or not to recommend patients who are under 50.

CHAIRPERSON WEISS: Dr. Bradley.

DR. BRADLEY: Yeah. I think Alice is correct but I think the warning could be one not simply of saying we discourage the use of this lens for people under age 50 but explain why. It's an issue of pupil size. Clearly then if a patient comes along with a small eight-year-old size pupil in a 20-year-old eye, then you could --

CHAIRPERSON WEISS: Then to play devil's advocate, if you are concerned about the age is not the age but the pupil size, why don't we just go back to Dr. Matoba's initial suggestion to ask the sponsor to provide the data of satisfaction correlating with the pupil size rather than eliminating a 30-year-old with a 3 millimeter

pupil.

Dr. Bradley.

DR. BRADLEY: For the reason I made, that it is unlikely that the data exist because there are so --

CHAIRPERSON WEISS: We can ask the sponsors here. We can ask the sponsor. Sponsor, does this data exist?

DR. BRADLEY: So the question to the sponsor would be then how many patients had 7 millimeter pupils. My guess is in this age group not many.

CHAIRPERSON WEISS: Dr. Rosenthal.

DR. ROSENTHAL: Rosenthal. I just wondered if I could ask the panel what if you had an 80-year-old eye with a 20-year-old pupil.

CHAIRPERSON WEISS: I'm in total agreement with you. We should be confining our comments to -- if the age issue is solely dependent on the pupil problem and not Dr. McMahon's concern about the lens moving back and forth and perhaps causing CME and uveitis which is a separate

problem.

If your concern is solely based on the pupil, then you have to talk about what you want to talk about which is the pupil. The sponsor will let us know how many large pupils did you have in the study.

DR. GORDON: Pupil size measurements were made for the contrast to the substudy. We will have to go back and look at that. We had some very small pupils and pupils up to 7 millimeters. The stratification that we performed in comparing the results both with and without the glare source showed no differences in that controlled testing.

CHAIRPERSON WEISS: So specifically for glare we don't know the number of large pupils and small pupils. I don't know if you can provide us while you are here today or otherwise you will provide it to the agency at a later date. Basically there was no correlation even if you had small numbers. Is that correct?

DR. GORDON: There was no correlation. We're looking it up so we'll get back to you.

CHAIRPERSON WEISS: Okay. That's fine. Thank you.

Are you satisfied, Dr. Bradley? Maybe that's an open question. Maybe I shouldn't have asked that. Perhaps we should go on.

DR. BRADLEY: Next.

CHAIRPERSON WEISS: Dr. Grimmett.

DR. GRIMMETT: Dr. Grimmett. Dr. Matoba's point is well taken. I am most interested in getting after mydriasis issues with this lens. That is obviously the key issue to me and I think Dr. Bradley agrees with that.

Based on the comments of the sponsor, I don't think they have the data Dr. Matoba is asking for. She is asking for patient satisfaction data such as that nighttime difficulty stuff associated with stratification of pupil sizes.

I just don't think that was done. I just strongly urge the panel to have some type of statement regarding pupil size and the visual aberrations we know that happens when light is passing through an aphakic section of the entrance

pupil.

CHAIRPERSON WEISS: If sponsor has any other comments on this issue, I would appreciate it.

DR. GORDON: We'll have to come back to you. We'll come back to the FDA with the exact numbers. I don't have the numbers on the distribution but we do have that information.

CHAIRPERSON WEISS: Okay. Fine. So we have a bit of -- I think everyone is in agreement that we do want extra data from the sponsor as far as patient satisfaction and how this relates to pupil size.

I think there is a small majority, at least there was five minutes ago, for saying this is not recommended for younger patients. The folks who voted, I guess that -- the people who voted, did anyone change their vote on the basis of this discussion or have all the votes stayed the same?

Dr. Bradley.

DR. BRADLEY: I think my vote stays exactly the same but I think the discussion

clarified the issue. The issue is not one of age. It's a matter of pupil size so maybe it could be reworded to emphasize the importance of pupil size.

CHAIRPERSON WEISS: So actually that is changing it because we were specifically -- this statement was specifically targeted at age, not pupil size. I think you have changed your vote, in which case that statement would come out.

Dr. Grimmett.

DR. GRIMMETT: Dr. Grimmett. I think there were two parts to the age comment. Part A was that this lens has not been studied in patients younger than 50. I think everyone will agree that is a statement of fact.

Part B was this lens is not recommended for patients under age 50 so I think the discussion now I would -- for all the reasons cited you can have a 20-year-old pupil and an 80-year-old patient as Dr. Rosenthal pointed out.

I would agree that I am most interested in pointing out the dim illumination mydriasis issue versus the lens optic rather than making an

age cutoff. I would vote take out Part B if we have the other issue stated.

CHAIRPERSON WEISS: I have been told the agency gets it which I think is a hint to me to move on.

I do want to just go through the labeling and clarify which of these will be in the physician labeling, which will be in the patient labeling, and which will be in both because there are two sets. Table 10.3, 10.5, and 10.7, would that be in both physician and patient labeling?

DR. HO: Allen Ho. I do think that's valuable for the patient. If I may add, for patient labeling I would like to make a suggestion. I think Anne Coleman had suggested in Attachment 2, right-hand column, the sentence, "Almost all of the study patients could pass their driver's test," etc., which I think is misleading because it's a very strong statement.

But deleting that statement actually forces the patient to go to a table and not all patients will go to a table. I think a way to

soften that would be to maintain the statement but delete almost all and start it with study patients and put in percentages.

CHAIRPERSON WEISS: Actually, I think I had criticized that because it's not that they can pass a driver's test now and they have the skill to drive, it's that they have a visual acuity of a certain level that will allow you to pass a driver's test.

DR. HO: In particular, the near vision test, the percentage of patients that can do that without glasses, I think, is valuable adjunct to that which is included in the table. My fear is that patients aren't going to look at a table and I like it in the text.

CHAIRPERSON WEISS: Perhaps -- okay. I'm still going to go back because I just want to finish the one item with the tables and then go on to a separate issue which is a statement to the patients in terms of what their functional visual acuity will be.

Table 10.3 is a bilateral patient survey

wearing spectacles during waking hours and to see at night. Table 10.5 is activities without spectacles. Table 10.7 is difficulty with night activity. I think these can be included in both patient and physician.

The comment that you were making, Dr. Ho, in terms of a summary statement as far as what your functional visual acuity is, I think you would like something a little bit more than this table. We do have something down here indicating that for many near vision tasks many patients still needed glasses. You would like something indicating that the majority of patients had visual acuity at distance which was good enough to drive without glasses.

DR. HO: No. I'm speaking specifically to the patient labeling, the last sentence of the first page. There was a recommendation to delete that sentence. I think we can -- I think it's valuable but I think it's misleading.

My recommendation would be to delete "almost all of the" and start the sentence with,

"Study patients could achieve driving vision" instead of "pass driving test." In parentheses, "Shop or apply their makeup (X percent.)" Or, "Read newspaper without glasses or contact lenses (X percent.) I think that is valuable information that is extracting it from the table and putting it into text.

CHAIRPERSON WEISS: That sounds like a good suggestion to me. Any thoughts on that? If not, then if we could include that as well. You would like that specifically for the patient labeling just to change the last sentence and put in statistics, percentages.

Another item was result may not be as good if only one eye is implanted with the lens. Do we want that in physician labeling or in patient and physician labeling? Both I hear from Glenda Such.

Dr. McMahon.

DR. McMAHON: Do we really want to say it that way? It is an issue that we don't know what the results would be.

CHAIRPERSON WEISS: Actually it was about 18 percent difference in terms of the uncorrected near and distance.

DR. McMAHON: Yeah, but that's a unilateral case versus unilateral -- an aphakic situation versus a pseudophake with CrystaLens versus pseudophake with another type of lens.

CHAIRPERSON WEISS: We could have two statements or what would you propose? We could reflect the data. The question would be there is no information about how you do if you only have one lens implanted and the other eye is pseudophakic with a different lens.

DR. McMAHON: That would be my suggestion.

CHAIRPERSON WEISS: So break it up into two sentences? Patient and physician, one or the other or both?

DR. McMAHON: I guess I would err on both.

DR. YOUNG: I would concur both.

CHAIRPERSON WEISS: Glenda Such and Terri

Young both indicate they would like that in patient and physician labeling. Dr. Coleman is still scribing. Correct? That's why we call you the scribe. This has happened to me once before so I have a learning curve.

The third item. The YAG at less than 12 weeks or the results of YAG capsulotomy at less than 12 weeks is not known. Patient, physician, or both?

Dr. Young.

DR. YOUNG: I would say both. I wanted to stress that I know that's in the -- it's already written here but it is to stress that the accommodative performance isn't known.

The other issues that are listed as possible complications meaning lens decentration or possible repositioning of the lens which we already know to be true for YAG capsulotomies performed for posterior chamber intraocular lenses and standards lenses. It is the accommodative performance that we are not sure of.

CHAIRPERSON WEISS: The fact that

immersion method gives you a better success rate, that is already in physician's labeling?

DR. YOUNG: That is already in physician's labeling.

CHAIRPERSON WEISS: Do we want to put that in patient labeling? Fine. No patient's labeling, just physician's labeling. We are going to remove from the patient labeling the fact the lens moves backwards and forwards. I don't know if that was in physician's labeling.

I guess we could say it is in physician's labeling so -- yeah, it's in patient's labeling but if it's in physician's labeling I would presume the panel would want it removed from both. Am I correct on that? I see some nods. That means yes.

We have a suggestion that this lens was not used in patients -- this lens was only used in patients above the age of 50 and the results in patients younger are not known. Patient and physician labeling?

DR. HO: Yes.

CHAIRPERSON WEISS: I hear a yes from

Glenda Such and some affirmatives from Dr. Ho and Dr. Matoba.

Another suggestion, long-term stability of the hinge as well as the accommodative refractive effect have not been determined. This is physician labeling. Should it also be patient labeling?

MS. SUCH: Yes.

DR. HO: I hear from Glenda Such, our consumer representative, yes. I see some affirmative nods.

DR. BRADLEY: Could you clarify the second part of that?

CHAIRPERSON WEISS: The second part was basically referring to question 2 of the agency that the stability of the hinge and the stability of the accommodative refractor effect, the long-term stability of these have not been either looked at or shown or demonstrated, whatever. That is going to be in both.

The indication that for near vision many patients still required for close visual tasks for

near vision and however you want to wordsmith it, many patients still will require glasses. Patient or physician or both? Both.

The claim of accommodation of one diopter. Patient, physician, or both that this lens is capable of accommodation of one diopter? Glenda.

MS. SUCH: I don't think it has to go on the patient.

DR. McMAHON: Neither.

CHAIRPERSON WEISS: Dr. McMahon agrees. That will just be physician labeling.

DR. McMAHON: No, I said neither.

CHAIRPERSON WEISS: Oh, neither.

DR. HO: I would agree with that.

CHAIRPERSON WEISS: I think Glenda Such just felt that should not go in patient labeling, I presume because the issue of one diopter and such would require more explanation.

Dr. McMahon didn't feel that it should go in either. I will direct you back to -- that was actually question 1(a) of the agency. Any other

comments on this one?

Dr. Bradley and then Dr. Matoba.

DR. BRADLEY: I think that should be put in there. I think that the evidence that we have currently seems to indicate that maybe about one diopter of accommodation. I think that's what the physicians want to know.

CHAIRPERSON WEISS: Dr. Matoba and then Dr. Grimmett.

DR. MATOBA: I agree with Dr. Bradley but I would like to ask Dr. McMahon why he thinks it should not be in there.

DR. McMAHON: Because I'm not fully convinced of accommodation.

CHAIRPERSON WEISS: You're consistent. This is good.

DR. McMAHON: I lost that vote before.

CHAIRPERSON WEISS: The fact that the only powers that were looked at were 16.5 to 27.5, that will be physician's labeling. Should that be in patient's labeling? No from Dr. Grimmett and no from Dr. Coleman. That would be physician

labeling. I assume that someone is going to propose and Dr. Matoba has brought this up of getting the data about pupil size and patient satisfaction and the issue of not being recommended for patients less than 50 I think was removed. Is that correct? That was removed.

Dr. Bradley.

DR. BRADLEY: There was a suggestion that it be replaced by a pupil size issue.

CHAIRPERSON WEISS: Well, correct me if I'm wrong. I believe that what the decision was was to get data and then have the agency make the recommendations on the basis of the data.

Dr. Bradley.

DR. BRADLEY: No. I think what happened was our original suggestion by Dr. Grimmett was modified but the sentiment was still there that some warning about the issue of people size should be included. Perhaps it's worth taking another vote on that because that did get lost I think.

CHAIRPERSON WEISS: Perhaps you can give the statement that would make you happy and then we

can have a vote on it.

Dr. Grimmett. It doesn't have to be exact.

DR. GRIMMETT: FDA can wordsmith it. I mean, just the sentiment that we can vote on should there be a pupil size warning with a lens optic 4.5. Do people agree with that if the FDA wordsmiths an appropriate statement? Is anyone against that?

CHAIRPERSON WEISS: Does everyone -- can we have a show of hands for those of you who would like a warning statement for a pupil size depending on what the data is like or not depending on the data? What if the data shows that there is no correlation?

DR. GRIMMETT: Well, sure. I don't think there is any data but if the data shows something, clearly go with the data. If there is no data, then I think there should be a pupil size warning statement.

CHAIRPERSON WEISS: Okay. Dr. Bradley agrees with that. Let me rephrase this. What the

intent is is still to have the sponsor come to the agency with data, any data they have, on large pupil sizes.

If that data does indeed show that pupil size was not at all related to patient satisfaction so that the concern of some of the panel members with a small size 4.5 optic is unfounded, then there would not be an additional warning here. But if either the data obviously showed that there was a problem or that the data was insufficient, then - -

Donna Lochner.

MS. LOCHNER: I just wanted to mention that we currently have a requirement that lenses that are less than 5.5 millimeter, we require sponsors to put a warning in their labeling that physicians should consider the effects of pupil size. That discussion is wonderful.

CHAIRPERSON WEISS: So, in other words, that was going to go on there anyway.

MS. LOCHNER: Right.

CHAIRPERSON WEISS: Okay. Rolling right

along.

PARTICIPANT: Thank you, Ms. Lochner.

DR. HO: Were you holding out for a reason?

CHAIRPERSON WEISS: I think you like our company. Dr. Coleman or anyone else, were there any other labeling issues?

Mr. McCarley.

MR. McCARLEY: From the dark side, I guess. Mr. McCarley with Ophtec and the consumer rep. My question is this seems to be, and correct me if I'm wrong, FDA, please, this is the second cataract product that will have patient labeling. The array multifocal that came before and then this one. Is that correct?

DR. ROSENTHAL: Rosenthal. That's correct.

MR. McCARLEY: Okay. It seems to me that now the patient is choosing which lens goes into the eye. I guess I understood the rationale behind the array lens is because they were potential safety issues and this one seems to be more on

efficacy.

CHAIRPERSON WEISS: In this case the sponsor has given us this labeling for the patient so we are not suggesting it to them.

DR. ROSENTHAL: This is Rosenthal. The sponsor gave it to us at our suggestion.

CHAIRPERSON WEISS: Oh. Okay.

DR. ROSENTHAL: It was our experts in some other branch, some other division, some other world that we work with, another office that really felt that it should be there for the patient to be able to understand the various issues related to this revolutionary concept.

MR. McCARLEY: Okay. And given that, should there be a comparative analysis or comparative information in the patient labeling because you don't have cataract surgery every day so the patient that opens it up and they don't have anything to compare it to.

DR. ROSENTHAL: Absolutely not because the lens is not compared to all the other ones.

MR. McCARLEY: Right. Well, my point is

how does the patient understand the one shot of the data rather than understanding what it's compared to like a standard --

DR. ROSENTHAL: The same way that every laser hands out patient labeling regarding its laser. We don't do a consumer report on various devices. We just make decisions on single devices and it was the recommendation of our experts the patient labeling be provided.

CHAIRPERSON WEISS: I'm going to ask Glenda Such, our consumer representative, to make a comment.

MS. SUCH: I would probably have a comment on this one. Yes, as in any product there is going to be things changing all the time so having something in the labeling would be like really, really horrible to have that has just the one product. You know that's going to change.

Sorry, but it will change. They are going to have to do like they do with everything else. They are going to have to compare products. This is part of how they are going to do it by

being able to look up these type of patient information pieces.

CHAIRPERSON WEISS: Are there any other issues concerning labeling? Does the agency have any issues? Otherwise, we'll go on to the -- otherwise, I believe we go on to the --

DR. ROSENTHAL: Question 4. Rosenthal.

CHAIRPERSON WEISS: Yes, Dr. Rosenthal.

DR. ROSENTHAL: Question 4, I think.

CHAIRPERSON WEISS: Question 4. Excuse me.

4. Do the data in PMA P030002 support the proposed indication statement?

o Primary implantation for the visual correction of aphakia in adult patients with cataracts.

o Provide improved near, intermediate, and distance vision without spectacles.

Any comments on this or should we just put it to how many of the panel members agree with this indication? Can you raise your hand if you agree? So we have Dr. Coleman agreeing, Dr.

Bradley agreeing, and Dr. McMahon agreeing, and Dr. Ho and Dr. Matoba agreeing. And Dr. Grimmett wants clarification.

DR. GRIMMETT: Dr. Grimmett. Dr. Bradley, didn't you make an earlier point which I thought was valid that the lens provides without spectacles improved intermediate and distance? Then you had a comment that near wasn't up to snuff and you had a way of phrasing that. Wouldn't that address the second half of the indication here?

CHAIRPERSON WEISS: Dr. Bradley.

DR. BRADLEY: Yeah. I think the point that I was making is that the sponsor has given us good evidence, I believe, that this lens will provide patients with well-focused, or I used the word, clear vision at distance and at intermediate, but not at near. However, the quality of vision at near is clearly superior to that provided by the standard lens. That was their statement.

CHAIRPERSON WEISS: Dr. Bradley, though - -

DR. GRIMMETT: Should then that second

part be modified or no?

DR. BRADLEY: Well, the crux of that statement and perhaps your query is the issue of improved relative to what? Improved intermediate and distance vision? Many of these patients obviously started off with a cataract and many of them started off with a refractive error so, sure, it's improved.

Improved near? Sure. Most of these patients started off with presbyopia so it seems to be improved. It's one of those statements which if you water down the statement enough, yeah, it's going to be true.

It depends on how people interpret it. The concern that I have that I mentioned very early on was that the sponsor today stated in their conclusion that this lens provided clear vision at these distances.

CHAIRPERSON WEISS: They are shaking their head. I think they -- well, perhaps I could have -- you can come to the podium and answer that, Judy.

DR. GORDON: Maybe I can clarify.

CHAIRPERSON WEISS: Yes.

DR. GORDON: The use of the word clear was a generic term at the end of the presentation and much has been made of it that is not implied in the indication, in the labeling, or anywhere in the PMA application.

CHAIRPERSON WEISS: Just for their blood pressure and just for the length of the meeting, let's just take out the word clear. That is going to be banished from this room for the next hour or two. Let's address ourselves to the indications that they have written here which are basically provide improved near, intermediate, and distance vision without spectacles.

Dr. Matoba.

DR. MATOBA: Can we provide these up? Has everyone agreed that the first is okay?

CHAIRPERSON WEISS: We can do whatever we want. Would you like to -- why don't we do that and let's break it up as Dr. Matoba has suggested into the indication, "Primary implantation for

visual correction of aphakia in adult patients with cataracts." Can we have a vote for those panel members who would agree with that? So we have a unanimous vote on the first portion of No. 4.

Dr. Matoba.

DR. MATOBA: If the patient is aphakic, I mean, has had a previous cataract extraction with an intact capsule. Would dialogue not be indicated in that patient?

DR. GRIMMETT: Dr. Grimmett. You might not be able to get it in the bag.

DR. MATOBA: It has to be captured.

DR. GRIMMETT: It has to be bag fixated according to their prior statements.

DR. MATOBA: Adults patients, do you want to say anything about the age at this point?

CHAIRPERSON WEISS: Dr. Rosenthal.

DR. ROSENTHAL: No, please. We have a standard way of describing it.

DR. MATOBA: Oh, okay. We only have to address ourself to these two statements and if one of these statements is not agreed to by a majority

of the panel, then this could be crafted in a way that the panel members would find it helpful or more honest or more representative of this PMA but we don't have to add extra information.

The conditions will address those issues such as age and such. I think the panel does agree with the first statement of primary implantation. Now we'll address ourselves to the second statement. I would like to have a vote for those panel members who agree with the second statement that the indication here has been shown that this does provide improved near, intermediate, and distance vision without spectacles.

Can we have those panel members that agree with that raising their hands? We have Dr. Coleman, Dr. Ho, Dr. Bradley, Dr. Grimmett, Dr. Young, and Dr. McMahon, and Dr. Matoba. I think that has just become unanimous for reasons unclear why it wasn't before but, hey. Time I'm told.

I think then we have answered question No. 4 and I want to know if there are any other additional issues the panel wants to raise or the

agency wants to raise. Otherwise, we will go on to the open public hearing.

Dr. Lepri, is that okay with you? Do you have anything else you would like us to address?

DR. LEPRI: I have nothing else.

CHAIRPERSON WEISS: You have nothing else for us to address. Good. We're going to go on to the open public hearing. Is there anyone who would like to make a relevant comment? I'm not sure why there was laughter but I'll just move on from there.

Seeing no relevant comments, or any irrelevant ones either, we will now go on to the FDA closing comments for five minutes. Does the FDA have any closing comments they want to make?

DR. ROSENTHAL: Rosenthal. No, we do not.

CHAIRPERSON WEISS: Dr. Rosenthal, thank you.

Would the sponsor like to add any closing comments? Yes.

DR. GLASSER: Adrian Glasser. Ladies and

gentlemen, members of the panel, and the FDA. I would like to thank you, first of all, for your very insightful review and comments on this presentation. I would like to dwell a little further on accommodation. I am paraphrasing Dr. Bradley's comments and I am sure Dr. Bradley will correct me if I'm wrong.

I believe that the data has presented a demonstration of one diopter of actual accommodation or accommodative amplitude. I would ask you to consider the rhetorical question of how much accommodation is required in order to say that accommodation is present. After all, a small change in focus for a eight-year-old child is a large change in focus for an 80-year-old cataract patient. I would like to talk also a little about subjective and objective measurement of accommodation which I think is highly relevant here. Subject measurement of accommodation requires that the subject, the patient, report when blur is first perceive.

This is certainly influenced by many

factors, some of which have been discussed here today including depth of field, psychophysical factors such as blur sensitivity and contrast sensitivity because the subject must be able to identify when something is blurred.

It requires that the subject initiate the accommodative response. They must perceive blur and they must respond to that blur by accommodating. It also then, the subjective method, requires that the subject report on the level of blur perceived to identify the accommodative amplitude.

So in subjective measurement of accommodation it requires cooperation from the subject. It requires clear stimulus presentation. The subject must see the stimulus clearly. It requires the subject to initiate the accommodative response.

The object of measurement of accommodation, and here presented the ideal case, would require no participation from the subject, would require no self-initiated accommodative

response, and would utilize a totally objective accommodation measurement.

Drug-stimulated accommodation. We can ask the question how can accommodation be stimulated and measured totally objectively? Pharmacological stimulation of accommodation is an appropriate way of inducing an accommodative response. It does not require that the subject initiate the accommodative response. An objective techniques would then ideally be used to measure the accommodative change.

I contend that this is perhaps the most appropriate way of objectively demonstrating whether or not accommodation occurs. Dr. Paul Kaufman from the Department of Ophthalmology at Madison University in a recent editorial in the Blue Journal of Ophthalmology identified that the use of 6 percent -- and I paraphrase him here -- identified that the use of 6 percent pilocarpine is an objective method to stimulate accommodation and cyclopentolate to cycloplegia accommodation, and then to use an objective technique to measure the

induced change.

This is exactly what was done in the study presented here today in 10 eyes of five patients in the substudy where an object of technique, namely A-scan ultrasound, was used to measure the movement of the IOL.

The A-scan measurements of forward movement of the CrystaLens in nine out of 10 eyes provides support for the claim that this lens moves forward in the eye with the stimulation of accommodation.

The near acuity data measured through the distance correction show a significantly greater proportion of CrystaLens implanted eyes with functional near vision at all acuity levels as compared to a standard IOL.

CrystaLens subject required a mean near add of 1.2 diopters less to achieve best near visual acuity than the standard IOL subjects. The data served to establish the functional accommodation provided by the CrystaLens.

The patient survey data are a very

important assessment of the satisfaction of the patients and it identifies that 93.8 percent of the CrystaLens patients performed most daily tasks without spectacle correction.

Indeed, as many as 77.5 percent read most things without spectacles. When asked how often they wear spectacles, 73.5 percent identify that they never wear spectacles or wear them almost none of the time.

In summary, the objective measurements of change in anterior chamber depth show forward movement of the lens. The near and intermediate visual acuity measured through the distance correction provide evidence of accommodation consistent with the proposed mechanism of action and the objective measurements.

This is further corroborated by the fact that the CrystaLens subjects required less add to achieve best corrected near acuity than subjects implanted with standard intraocular lenses.

This is the first accommodating IOL to be presented for review by the panel. I believe this

is a unique opportunity for an exciting and significant technological development. This may set the stage for future significant developments in cataract surgery beyond simply restoring distance acuity and near acuity.

Much work remains to be done to fully understand and characterize pseudophake accommodation. There will no doubt be significant future developments in this fast evolving field. However, we believe that the data presented here offered the first real and compelling evidence in support of the notion that accommodation can be restored after cataract surgery with an accommodating intraocular lens.

We would like to thank the panel and the FDA for their interest and assistance in bringing the CrystaLens to the panel for consideration. Thank you very much.

CHAIRPERSON WEISS: I would just to thank the sponsor for their very clear presentation and the panel members and the agency for also elucidating this PMA for us.

We will be moving on now to voting options which Sally Thornton will now read.

EXECUTIVE SECRETARY THORNTON: The medical device amendments to the Federal Food, Drug, and Cosmetic Act is 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 designed 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. Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions on intended use outweigh any probably risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended usages and conditions of use when labeled will

provide clinically significant results. Your recommendation options for the vote are as follows:

First, approval if there are no conditions attached.

Second, 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, 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 if a reasonable assurance has not been given that the device is affective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting the chair will ask each panel member to present a brief statement outlining the reasons for their vote.

Thank you, Jayne.

CHAIRPERSON WEISS: Thank you. At this time I would like to ask for a motion to be made from the floor concerning this PMA from the panel.

Dr. Ho.

DR. HO: Approvable with conditions.

CHAIRPERSON WEISS: Can you state what you would like to be approvable with conditions? The motion would be if you agree with No. 4, then this is the indication.

DR. HO: That's correct.

CHAIRPERSON WEISS: Can you state that?

DR. HO: Well, why don't you read it?

EXECUTIVE SECRETARY THORNTON: No.

CHAIRPERSON WEISS: I can't state it for you so if you could just state what is written down.

DR. HO: I would move to make PMA P030002 approvable with conditions to support the proposed indication statement of primary implantation for the visual correction of aphakia in adults patients with cataracts to provide improved near, intermediate, and distance vision without

spectacles.

CHAIRPERSON WEISS: Is there a second of the motion?

DR. YOUNG: I second it.

CHAIRPERSON WEISS: Dr. Young seconds the motion. We would need to make a motion now to introduce each separate condition. That motion will then be seconded and voted on as they come up.

Dr. Coleman, can you introduce some of these conditions?

DR. COLEMAN: Some of them. I would recommend as a condition that we include tables 10.3, 10.5, and 10.7 in both the patient and physician labeling and making sure that we include percentages in the patient labeling in the last sentences on one of attachment 2.

CHAIRPERSON WEISS: Do we have a second of that?

DR. GRIMMETT: I second.

CHAIRPERSON WEISS: We have a second of that motion. I would like to then put this to a

vote. All of the panel members who would like to vote in the affirmative, please raise their hand.

This is just for -- we are going to go through each of the conditions and then at the end we go through the PMA. This is for this particular condition. Dr. Grimmett, Dr. Young, Dr. McMahon, Dr. Bradley, Dr. Matoba, Dr. Ho, and Dr. Coleman have all voted yes.

Any other conditions, Dr. Coleman?

DR. COLEMAN: Second condition is that in patient physician labeling information on the effectiveness of YAG capsulotomy prior to 12 weeks has not been established to be included.

CHAIRPERSON WEISS: Can you restate that, please?

DR. COLEMAN: That information on the effectiveness of YAG capsulotomy prior to 12 weeks has not been established.

CHAIRPERSON WEISS: I believe that Dr. Young had put that condition forward and I think, and you can correct me if I'm wrong, is that her concern was the accommodative performance after YAG

capsulotomy that was performed at less than 12 weeks has not been established. Is that correct?

DR. YOUNG: That is correct.

DR. COLEMAN: We can amend mine that the effectiveness of accommodative ability after YAG capsulotomy prior to 12 weeks has not been established.

CHAIRPERSON WEISS: Does anyone second that?

DR. YOUNG: I second it.

CHAIRPERSON WEISS: Dr. Young seconds it. We will have a vote on that. All members who would like to vote in the affirmative, please raise your hand. All of those who would like to vote against, please raise your hand. All those who would like to abstain, please raise their hand. So Dr. Grimmett, Dr. Young, Dr. Bradley, Dr. Matoba, Dr. Ho, Dr. Coleman all vote in the affirmative and Dr. McMahon abstains.

DR. COLEMAN: The next condition is to not include in the patient label any information about the immersion biometry but to include it as

it is in the physician labeling.

CHAIRPERSON WEISS: Perhaps we don't even need that as a condition because it's already in the physician labeling.

DR. COLEMAN: The next condition is to remove the movement of the lens from the patient labeling.

CHAIRPERSON WEISS: Anyone second that condition?

DR. McMAHON: Second.

CHAIRPERSON WEISS: Dr. McMahon seconds. We will have a vote. All those who would like to vote in the affirmative, please raise your hand. This is unanimous. Dr. Coleman, Dr. Ho, Dr. Matoba, Dr. Bradley, Dr. McMahon, Dr. Young, and Dr. Grimmett.

DR. COLEMAN: Next condition is to mention that the visual results are not know if the CrystaLens is placed in one eye and the other eye is pseudophakic with another standard IOL in both patient and physician labeling.

CHAIRPERSON WEISS: Anyone second?

DR. McMAHON: Second.

CHAIRPERSON WEISS: Dr. McMahon seconds. Can we have a vote? All those who would like to agree, please raise your hand. It's unanimous.

DR. COLEMAN: The next condition is to include in both physician and patient labeling that information on subjects less than 50 years of age available or has not been studied.

CHAIRPERSON WEISS: Perhaps --

DR. COLEMAN: Subjects less than 50 years of age have not been studied with the CrystaLens as of this time.

CHAIRPERSON WEISS: Second?

DR. HO: Second.

CHAIRPERSON WEISS: Dr. Ho seconds. Can we have a vote? All those who would like to vote in the affirmative, raise your hand. This is unanimous. We can move on.

DR. COLEMAN: Include in both the patient and physician labeling that the long-term stability of the lens has not been established for the hinge or the accommodative refractive effect.

CHAIRPERSON WEISS: Second? Dr. Bradley seconds. Can all those who agree please raise your hand. This is unanimous as well.

DR. COLEMAN: Include in both physician and patient labeling that patients will require or may require glasses after the use of their CrystaLens for near, intermediate, or distance acuity.

CHAIRPERSON WEISS: Would you like to sort of reflect that this is more likely a problem at near than at distance or intermediate?

DR. COLEMAN: Yes. Patients may require glasses at near distance or intermediate acuity. However, it is more likely to be seen at near acuity.

DR. BRADLEY: We can work on the wording of that.

DR. COLEMAN: Yeah, the wordsmithing.

DR. HO: Spectacle requirement may be higher with near.

CHAIRPERSON WEISS: I'm told by Sally that the FDA basically understands what the panel

is trying to reflect so we don't have to wordsmith it. I think the concern is more near than at distance.

DR. COLEMAN: And that it would be in both the physician and patient labeling.

CHAIRPERSON WEISS: So with that sentiment, we are going to be voting on sentiment as opposed to words, could we have everyone who agrees please raise their hand? Unanimous. Maybe I should go for sentimental vote. It's quicker.

Okay. Yes?

DR. COLEMAN: Mention that there is approximately one diopter of accommodative ability in the physician label or accommodative amplitude of one diopter in the physician label.

CHAIRPERSON WEISS: Any seconds? Dr. Bradley seconds. A vote, please. Raise your hand if you agree. So we have Dr. Grimmett, Dr. Coleman, Dr. Matoba, and Dr. Bradley vote yes. All those who disagree? Dr. McMahon and Dr. Young and Dr. Ho vote no. Was there an abstention? No abstention.

EXECUTIVE SECRETARY THORNTON: Four to three.

CHAIRPERSON WEISS: Four to three. That would be passing. Any other?

DR. COLEMAN: Yes. To mention as a precaution that the range of axial lengths is 21 to 26.6 millimeters and the lens powers used in the study were 16.5 to 27.5 diopters.

CHAIRPERSON WEISS: And if you --

DR. COLEMAN: In the physician labeling.

CHAIRPERSON WEISS: Any second?

DR. HO: I second it.

CHAIRPERSON WEISS: Multiple seconds including Dr. Ho. Can we have a vote? All those agree raise your hand, please. This is unanimous. Next.

DR. COLEMAN: To mention on page 2 that atrophy sulfate 1 percent should be given immediately postoperating and postoperative day No. 1.

CHAIRPERSON WEISS: Physician or patient?

DR. COLEMAN: Physician labeling.

CHAIRPERSON WEISS: Do we have a second?

DR. YOUNG: Second.

CHAIRPERSON WEISS: Dr. Young seconds. Can we have a vote? All those agree, please raise your hand. This is unanimous.

DR. COLEMAN: To give a precaution that the effective vitrectomy on the performance of the lens is unknown in physician labeling.

DR. McMAHON: Second.

CHAIRPERSON WEISS: Seconded. Everyone who agrees, raise your hand. It is unanimous.

DR. COLEMAN: To also include under adverse events in the physician's labeling the possible increased risk of CME associated with sulcus-bag placement of the haptics.

CHAIRPERSON WEISS: A second do we have?

DR. HO: Second.

CHAIRPERSON WEISS: Dr. Ho seconds. All those who agree, please raise your hand. Dr. Young, Dr. McMahon, Dr. Coleman, Dr. Ho, Dr. Matoba, Dr. Bradley agree. All those who disagree raise your hand.

DR. GRIMMETT: Abstain.

CHAIRPERSON WEISS: And all those who abstain. We were getting to you, Mike. Those who abstain, Dr. Grimmett abstains.

DR. COLEMAN: To include in the physician's label the information on stability of near, intermediate, and distance acuity looking at less than or minus half a diopter change of MSRE over a year.

CHAIRPERSON WEISS: I'm not clear what that condition is.

DR. COLEMAN: That was to include those tables on the stability of the near distance and intermediate acuity where they could see how the dioptric changes in terms of percentages of those that had less than a half diopter from forms three to four and then four to five.

CHAIRPERSON WEISS: Dr. Grimmett, we haven't seconded it so I think we can discuss it.

DR. GRIMMETT: Sponsor agreed to that in their response to your concerns when you stated it in your --

DR. COLEMAN: Right. We don't have to vote on it then?

CHAIRPERSON WEISS: Well, if they agree, the we're not altering what they want to do so we don't have to add that.

DR. COLEMAN: Okay. To mention in the physician's and patient's labeling that pupil size is important in terms of --

CHAIRPERSON WEISS: I think we don't have to mention that because that is part of the agency's protocol anyway. I would -- there is one thing that I think that we should discuss --

DR. COLEMAN: The study. Sorry, this is my last one. That the sponsor will get back to the FDA with information about pupil size and stratification on pupil size and the satisfaction surveys.

CHAIRPERSON WEISS: Fine. Do I have a second for that?

DR. GRIMMETT: Yes.

CHAIRPERSON WEISS: Dr. Grimmett seconds. Can I have a vote? Everyone votes in the

affirmative, please raise your hand. That's unanimous. The only other one that I have here that I can see is that the visual acuity may not be as good if you have your phakic in one eye and you only have the CrystaLens placed in the other eye. I think that was a table that we talked about including.

DR. COLEMAN: To include the information that subjects that had the primary implant were about 80 percent uncorrected near acuity. Those that had bilateral implantation around 97 percent.

CHAIRPERSON WEISS: Do we have a second for that? Dr. Matoba seconds. Can we have a vote? Everyone who agrees, please raise your hand. This is unanimous. Are there any other conditions, Dr. Coleman, or any of the other panel members?

We will now have a final vote. Would all in favor of the main motion with its condition signify by raising their hand? The PMA passes unanimously. That is, this PMA is approvable with conditions.

I will now poll each of the individual

panel members to ask them to give us the reasons why they voted affirmative.

Dr. Coleman.

DR. COLEMAN: I believe that there is reasonable assurance of safety and effectiveness of the CrystaLens.

CHAIRPERSON WEISS: Thank you.

Dr. Ho.

DR. HO: I would first like to thank the sponsors for presenting a clear dataset and a concise presentation. I thought they did an excellent job.

I do think that this is a safe and I'm excited about the prospects of evaluating patients who have this in. I do think it can be, in their words, revolutionary and efficacious.

I have a little trouble with the issue of accommodation. That may be my lack of understanding of the issue, although I think it's a very complicated subject. I think there is a suggestion that their may be an accommodative effect but I think an N of 5 to 10, that's

underwhelming and not substantial enough for me to include accommodating in the language. Otherwise, I do think this is approvable with our conditions specified.

CHAIRPERSON WEISS: Dr. Matoba.

DR. MATOBA: Alice Matoba. I felt that from the patient's point of view there was adequate evidence of efficacy and safety.

CHAIRPERSON WEISS: Dr. Bradley.

DR. BRADLEY: I think is an exciting new product. I was disappointed with the quality of the data but I think it is demonstrated efficacy, although somewhat marginally so. That's what I voted to approve.

CHAIRPERSON WEISS: Dr. McMahon.

DR. McMAHON: First of all, even though I've been rather tough all day on this accommodation business, I do want to acknowledge and thank the sponsor for a generally well done presentation both of the sponsors themselves, the consultants, and the investigations. It's always much easier when there is a well-organized study

when we have to read these volumes and volumes of document. I certainly appreciate the organization of the study.

I vote for approval with conditions from the point if view that I still have some concerns about this business about true measurement of accommodation under nonpharmacologic circumstances. I do not buy the argument that Paul Kaufman's suggestion is the best way to do that. I would flatly disagree with that.

I think it would be in the sponsor's best interest for all of us to actually have that answer what this really does accommodate, if there really is true accommodation or not.

I think the lens is safe. I still have a little bit of anxiety with regard to a lens moving in the eye over a period of decades as to what that's going to do. The data at this point is supportive of it.

The visual acuity information I think is quite impressive. That is the principle reason that I voted for it.

CHAIRPERSON WEISS: Dr. Young.

DR. YOUNG: I also concur that there is a reasonable assurance of safety and efficacy. The issues of accommodation are murky. As a pediatric ophthalmologist I see this as a prototype, if you will, as good potential for pediatric patients with amblyopia. I applaud the sponsors for their excellent presentation.

CHAIRPERSON WEISS: Dr. Grimmett.

DR. GRIMMETT: Dr. Grimmett. I would also like to thank the sponsor for a thorough and clear presentation. I voted approval of the conditions because the application showed me reasonable assurance of safety and effectiveness. Thanks again.

CHAIRPERSON WEISS: We are going to have any comments from Glenda Such and Mr. McCarley.

MS. SUCH: Glenda Such here. As consumer representative I don't vote but I would concur and I would have voted in favor if I could have. I think that the study was well put together and I think the comments that were made and the issues

that were addressed were ones that I myself would have had. I think a job well done was done today.

CHAIRPERSON WEISS: Mr. McCarley.

MR. McCARLEY: This is Rick McCarley. I don't have anything else to add.

CHAIRPERSON WEISS: Well, thank you. I think PMA PO30002 has been dealt with. I would like to thank the sponsor for an excellent presentation and as well the agency and the panel.

Before we conclude, Sally Thornton may have some remarks.

EXECUTIVE SECRETARY THORNTON: I just wanted to thank the panel for their review of this document and the time they spent here and abroad reviewing it.

I also wanted to make the announcement that we have canceled the July panel meeting so that should be up on the web shortly but I wanted you all to know today. Thank you very much and have a very safe holiday.

(Whereupon, at 3:02 p.m. the meeting was adjourned.)