

UNITED STATES OF AMERICA  
 DEPARTMENT OF HEALTH AND HUMAN SERVICES  
 FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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OPHTHALMIC DEVICES PANEL

+ + +

April 8, 2013  
 8:30 a.m.

Hilton Washington, D.C. North  
 620 Perry Parkway  
 Gaithersburg, Maryland

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JEREMIAH BROWN, JR., M.S., M.D.	Voting Member
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CYNTHIA OWSLEY, Ph.D., M.S.P.H.	Voting Member
THOMAS L. STEINEMANN, M.D.	Voting Member
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JOANNE F. SHEN, M.D.	Temporary Voting Member
BARBARA D. BERNEY	Patient Representative
LAWRENCE E. LEGUIRE, Ph.D., M.B.A.	Consumer Representative
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MEETING

(8:30 a.m.)

DR. HIGGINBOTHAM: Good morning. I would like to call this meeting of the Ophthalmic Devices Panel of the Medical Devices Advisory Panel to order. I am Dr. Eve Higginbotham, the Chair of this Panel. I am a glaucoma specialist, Professor of Ophthalmology at Emory University, and I am happy to serve today as your Chair.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application sponsored by Bausch & Lomb for the Trulign Toric Accommodating Posterior Chamber Intraocular Lens.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position, and affiliation. I'd like to start with Dr. Eydelman.

DR. EYDELMAN: Good morning. My name is Dr. Malvina Eydelman, and I'm the Division Director for the Division of Ophthalmic and Ear, Nose and Throat Devices here at the FDA.

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DR. CLAYTON: Good morning. My name is Janine Clayton. I'm the Director of the Office of Research on Women's Health at the National Institutes of Health, and I'm a cornea and uveitis specialist.

DR. SHEN: Good morning. I'm Joanne Shen. I'm a cornea and external disease specialist at the Mayo Clinic Branch in Scottsdale, Arizona, assistant professor.

DR. HARRIS: Good morning. My name is David Harris. I'm a cornea specialist and anterior segment specialist with the University of Tennessee with the Graduate School of Medicine in Knoxville, Tennessee and the Hamilton Eye Institute in Memphis, Tennessee.

DR. OWSLEY: Good morning. My name is Cynthia Owsley. I'm Professor of Ophthalmology at the University of Alabama at Birmingham, and my research area is aging-related eye disease and vision impairment.

DR. EVANS: Good morning. I'm Scott Evans, Senior Research Scientist, Biostatistics, at Harvard University. My expertise is in clinical trials.

DR. BROWN: Good morning. I'm Jeremiah Brown. I am a retina specialist in San Antonio, Texas, Clinical Associate Professor of Ophthalmology at the University of Texas Health Science Center in San Antonio.

DR. KIM: Good morning. My name is Joung Kim. I'm a cornea and external disease specialist at the Emory Eye Center in Atlanta, Georgia.

MS. FACEY: Natasha Facey, Designated Federal Officer for the

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Ophthalmic Devices Panel.

DR. BRESSLER: Good morning. I'm Neil Bressler. I'm a Professor of Ophthalmology at Johns Hopkins University School of Medicine and specialist in retina.

DR. BRADLEY: Good morning. I'm Arthur Bradley, Professor of Vision Science from Indiana University.

DR. COLEMAN: Good morning. I'm Anne Coleman, Professor of Ophthalmology and Epidemiology at UCLA, and I'm a glaucoma specialist.

DR. STEINEMANN: Hi, I'm Tim Steinemann. I'm a cornea and cataract specialist at MetroHealth Medical Center in Cleveland, Ohio. I'm a Professor of Ophthalmology at Case Western Reserve in Cleveland. Thank you.

DR. FELDMAN: Good morning. I'm Brad Feldman. I'm a cornea, cataract, and refraction specialist in Philadelphia, and I serve at the Wills Eye Institute. Thank you.

MS. BERNEY: Good morning. I am the Patient Representative to this Panel, and I am an artist, and I represent the Vision Surgery Rehab Network.

DR. HIGGINBOTHAM: And your name?

MS. BERNEY: Barbara Berney.

DR. LEGUIRE: Good morning. Larry Leguire. I'm the Consumer Representative and retired former Director of Electrophysiological Testing in

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Eye Research at Nationwide Children's Hospital, Department of Ophthalmology.

DR. TARANTINO: Good morning. My name is Nick Tarantino. I am the Industry Representative and Vice President of Clinical Research and Regulatory Affairs for HOYA Surgical Optics.

DR. HIGGINBOTHAM: Thank you very much, and thank you all for being here today. If you have not already done so, please sign the attendance sheets that are on the tables by the doors outside.

Ms. Natasha Facey, the Designated Federal Officer for the Ophthalmic Devices Panel, will make some introductory remarks.

MS. FACEY: The Food and Drug Administration is convening today's meeting of the Ophthalmic Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other Agencies and are subject to Federal conflict of interest laws and regulations.

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

FDA has determined that members and consultants of this

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Panel are in compliance with the Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees and regular Federal employees who have financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

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

For today's agenda, the Panel will discuss, make recommendations, and vote on information regarding the premarket approval application sponsored by Bausch & Lomb for the Trulign Toric Accommodating Posterior Chamber Intraocular Lens. The Trulign Toric Accommodating IOL is intended for primary implantation in the capsular bag of the eye for visual correction of aphakia and postoperative refractive astigmatism secondary to removal of a cataractous lens in patients -- excuse me -- in adult patients with or without presbyopia who desire improved uncorrected distance vision and reduction of residual refractive cylinder. The

Trulign Toric Accommodating IOL provides approximately one diopter of monocular accommodation, which allows for near, intermediate, and distant vision without spectacles.

This meeting is classified as a particular matter involving specific parties.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, no conflict of interest waivers have been issued in connection with 18 U.S.C. Section 208.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. Nicholas Tarantino is serving as the Industry Representative, acting on behalf of related industry, and is employed by HOYA Surgical Optics.

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

Appointment to Temporary Voting Status. Pursuant to the

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authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for the duration of this meeting on April 8th, 2013.

Dr. Arthur Bradley, Dr. Joung Kim, Dr. Scott Evans,  
Dr. Brad Feldman, Dr. David Harris, Dr. Joanne Shen, Dr. Janine Clayton.

For the record, these individuals are special Government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. This has been signed by Dr. Jeffrey Shuren, Director, Center for Devices and Radiological Health on April 3rd, 2013.

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

Transcripts of today's meeting will be available by Free State Court Reporting, Incorporated. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

The press contact for today's meeting is Synim Rivers.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is in the area beyond the speaker's podium. I request that reporters please wait to speak to FDA officials until after the panel meeting has concluded.

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If you are presenting in the Open Public Hearing Session today and have not previously provided an electronic copy of your slide presentation to the FDA, please arrange to do so with AnnMarie Williams at the registration desk.

In order to help the transcriber identify who is speaking, please be sure to identify yourself each and every time.

Finally, please silence your cell phones and other electronic devices at this time. Thank you.

Dr. Higginbotham?

DR. HIGGINBOTHAM: Thank you, Ms. Facey. We will now proceed with updates from the FDA. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

FDA?

DR. EYDELMAN: Thank you, Dr. Higginbotham.

I'm delighted to report that since the last division update in July of 2010, the following 13 individuals have joined my division, and their expertise is dedicated to reviewing ophthalmic devices, i.e., I'm not reviewing individuals -- I'm not presenting individuals who spend their time reviewing other kind of devices in my division. So for those individuals in the attendance, please stand up as I read your name.

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Charles Chiang received a B.S. in bioengineering at the University of Maryland, College Park. Prior to joining ODE in August 2011 as a scientific reviewer, he was a researcher at FDA's Office of Science and Engineering Laboratories. His research experience includes drug delivery with microspheres, blood coagulation, hemolysis, small-scale fermentation, and downstream processing. Thank you.

Dr. Sam Dahr, who is not here today, graduated from Stanford University with a B.S. in biological sciences and an M.S. in engineering economic systems. He then completed his medical degree as well as internship in internal medicine at the University of Oklahoma College of Medicine. Dr. Dahr completed his ophthalmology residency as well as fellowship in vitreoretinal surgery and ocular oncology at the University of Cincinnati in Cincinnati, Ohio.

Subsequently, Dr. Dahr held an appointment as a senior staff fellow at the National Eye Institute. During that time, he performed additional training in medical retinal diseases and participated in clinical trials for age-related macular degeneration and diabetic retinopathy. While at NEI, Dr. Dahr also trained in uveitis and ocular immunology, participating in clinical trials for the use of biologic agents in the treatment of uveitis. He has served as a consultant to the FDA for ophthalmic devices with a retinal indication since March of 2007, was named a medical device fellow in September 2011. As such, he is able to contribute to FDA's premarket review

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while practicing vitreoretinal diseases and surgery, uveitis and ocular oncology.

Dr. Dan Fedorko earned his bachelor's degree in biology from Virginia Tech and his master's and Ph.D. in clinical microbiology from the Medical College of Virginia. He did his postdoctoral fellowship in clinical microbiology at the Mayo Clinic. He has been a diplomate of the American Board of Medical Microbiology since '91. Before joining the FDA in June of 2012, he worked as a senior staff microbiologist at the National Institute of Health's clinical center. At the NIH, he performed research in diagnostic microbiology and infectious diseases and directed diagnostic testing in the parasitology, anaerobe and virology laboratories.

Dr. Denise Hampton has been selected as the Acting Branch Chief of the Contact Lenses and Retinal Device Branch in February of 2013. Dr. Hampton received her bachelor of science degree in biology from University of North Carolina in Chapel Hill in '95. She began her doctoral studies at the University of Virginia in '96 and received her Ph.D. in microbiology in 2004. Dr. Hampton completed a postdoctoral fellowship in the Laboratory of Allergic Diseases at the National Institute of Allergy and Infectious Diseases in 2006. Since September of '06, she has been working as a microbiology scientific reviewer in our division. We're delighted to welcome Denise into her new role.

Dr. Maggie Hymowitz, who is not here today, received her B.A.

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in biological basis of behavior from the University of Pennsylvania and her medical degree from Boston University. She completed her residency in ophthalmology at Montefiore Medical Center and then completed a clinical and surgical fellowship in glaucoma at Bascom Palmer Eye Institute.

Dr. Hymowitz is currently an attending ophthalmologist at the Wills Eye Institute at Philadelphia. Since December of 2012, Dr. Hymowitz has joined the FDA staff as a part-time medical device fellow.

Dr. Julie Kim received a B.A. in political science at Amherst College and an M.D. from New York Medical College and then completed residency at the New York Eye and Ear Infirmary. Dr. Kim completed her glaucoma fellowship at the Massachusetts Eye and Ear Infirmary. Prior to joining FDA, she has obtained experience as a clinical research coordinator for a medical device company and a CDC fellow in applied epidemiology. Since August of 2011, she has worked as a full-time medical officer in our division.

Ms. Claudine Krawczyk received her B.S. and master's in mechanical engineering from State University of New York at Buffalo. She first started with FDA in the Division of Ophthalmic Devices in '94 working in the Intraocular Devices Branch. After leaving FDA in 2000, she returned first as an ORISE fellow and subsequently as a medical device fellow. Since December of 2012, Claudine has joined our permanent staff once again. She brings a wealth of experience from her years with the FDA, including experience with IOLs, contact lenses, and glaucoma devices. We welcome

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her back.

Dr. Carol Lin has joined us as an FDA commissioner's fellow in November of 2012. Dr. Lin received her B.A. from Washington University in St. Louis in biology and medical degree from University of Maryland School of Medicine. She completed her ophthalmology training in New York Medical College and a glaucoma fellowship at the Mt. Sinai Hospital in New York. She was in clinical practice in Long Island, New York prior to joining the FDA.

Dr. Leonid Livshitz has joined us in October of 2012. He received his master's and Ph.D. in biomedical engineering from the Technion-Israel Institute of Technology. Subsequently, Dr. Livshitz worked as an R&D engineer for a medical device company. In 2004 he joined Cardiac Bioelectricity and Arrhythmia Center in the Case Western Reserve University as a postdoc fellow and subsequently became a research assistant professor in biomedical engineering in 2008. His research expertise includes computational modeling, biological signal processing, and bioelectromagnetics.

Dr. Maryam Mokhtarzadeh completed her undergraduate degree in chemistry at Princeton University and her M.D. from Johns Hopkins School of Medicine in 2004. She then trained as an ophthalmology resident at the Kresge Eye Institute and subsequently completed a postdoctoral fellowship in ocular surfaces disease and corneal transplantation at Jules Stein Eye Institute at UCLA. Maryam began her career at the FDA as a

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commissioner fellow in October of 2010. In November of 2011, she joined our division as a full-time medical officer.

Dr. Tieuvi Nguyen received her B.S. from University of Nebraska in biological systems engineering and her Ph.D. degree in biomedical engineering in the City College of New York. Her research training includes tissue engineering, mass transport modeling, animal studies, and vision science. Prior to joining us in October of 2011, Tieuvi obtained diverse professional experience in market research, private equity, management consulting, project management, and biotechnology in biomedical device sectors.

Dr. Michelle Tarver received a bachelor's degree in biochemistry from Spelman College in '95. She pursued an M.D./Ph.D. at Johns Hopkins School of Medicine and Bloomberg School of Public Health. Her Ph.D. was in clinical epidemiology. She completed a residency in ophthalmology in 2007 and a fellowship in uveitis in 2008, both at Johns Hopkins University Wilmer Eye Institute. She was on the uveitis faculty at Johns Hopkins School of Medicine prior to coming to the FDA. Dr. Tarver has expertise in uveitis as well as study design, conduct, and analysis. Dr. Tarver joined the division in July of 2011.

Ka Nam To graduated from the University of Maryland College Park in 2011 with a B.S. in bioengineering. His expertise area is electronics and software-based applications of medical devices. He is a reviewer in

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DOED's Diagnostic and Surgical Devices Branch. Prior to joining DOED in July of 2012, he was a program analyst with FDA's Office of Surveillance and Biometrics Medicine Program.

I'm delighted to welcome all of these outstanding individuals to my division and to introduce them to all of you today.

Now I would like to bring to your attention a couple of other important issues that have taken place recently, one of them being the reorganization of the Office of Devices which took place on November 1st of 2012. The intent behind the reorganization was to allow the branches to become more focused on less diverse devices and to be able to better manage our workload. A result of the reorganization was two new divisions and 12 new branches.

As you can see, prior to November of 2012, this division was named Division of Ophthalmic, Neurological, Ear, Nose and Throat Devices. Hence, our division was in charge all of the neurological, neurosurgical, and psychiatric devices in addition to ophthalmic and ENT devices, and this was our structure prior to November.

As the years went by, the number of submissions we received escalated drastically. So just to give you a feel for the workload, in FY2011, we had a total of 1385 submissions; in FY2012, we received 1,441 submissions, which was quite a significant amount to handle with the management staff that we had. Out of those, in 2012, only 447 were

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ophthalmics and 215 were ENT, and as you can see, neuro was the largest number of submissions in both 2011 and 2012.

Hence, once MDUFA allowed us some additional funding and promise of a reduced manager to staff ratio, we were able to split my division into two new divisions. So as you can see, on November 1, just seven reviewers were added from a different division, and the rest of the managers and reviewers came from my division, forming two new divisions, the current division of Ophthalmic and Ear, Nose and Throat Devices and a new division, which is the Division of Neurological and Physical Medicine.

The best news is that I was able to keep all of my outstanding reviewers that were dedicated to ophthalmic reviews in my division as well as all of my management staff stayed with my division. There was only one manager who was previously dedicated to neuro review, and she went to the new division, but the rest of the staff stayed here. So I am delighted I have a brand new division with -- by maintaining all of the expertise that we had.

Since we now had only ophthalmic and ENT devices, the other great perk was that we were able to formulate one new branch. So previously, we had only three branches dedicated to ophthalmic and ENT and one branch dedicated to neurology. In the new division, which currently is Division of Ophthalmic and Ear, Nose and Throat Devices, we have three branches dedicated just to ophthalmic devices and one branch dedicated to ENT devices. And now you will hear the update from the three branch chiefs.

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Here you go.

DR. KIANG: Good morning. My name is Dr. Tina Kiang, and I am the branch chief of the Intraocular and Corneal Implants Branch. I will be giving you an update on the branch activities since July of 2010.

Since our reorganization, this is our new -- this is a list of our new branch members, including those members who have been added since 2010. Our branch, since reorganization, reviews all IOL and accessories, glaucoma implants, OVDs, artificial eyes, punctal plugs, lacrimal stents, endocapsular rings, and tissue adhesives, just to name a few devices.

Since July of 2010, we have had a number of notable PMA approvals. On October 19th, 2010, FDA approved P100016 Aaren Scientific's EC3 Intraocular Lens and EC3 PAL IOL. It is indicated for primary implantation in the capsular bag of the eye for the visual correction of aphakia in adult patients in whom a cataractous lens has been removed. On June 25th, 2012, FDA approved P080030, Glaukos Corporation's iStent Trabecular Micro-Bypass Stent. It is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure, IOP, in adult patients with mild to moderate open-angle glaucoma currently treated with ocular hypotensive medication.

Finally, in July 2nd, 2012, FDA approved P110007 for Abbott Medical Optics Healon EndoCoat Ophthalmic Viscosurgical Device, or OVD. It is indicated for use as a surgical aid in patients undergoing ophthalmic

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anterior segment surgical procedures, including cataract surgery with an intraocular lens, cataract surgery without an intraocular lens, and secondary intraocular lens implantation.

In addition to our device reviews, we are also involved in a number of ophthalmic device initiatives. We are dedicated to improving clinical trials in our work with both developing -- in helping developing international and national standards and into developing FDA guidance.

In addition, over the past several years, we have been conducting research to develop new tools to assess the safety and performance of ophthalmic devices under certain conditions. In particular importance in our branch was the issue of tasks. A number of our staff are heavily involved in the development of national and international standards. To that end, since July of 2010, we have recognized this list of standards shown on the slide for most -- all of which are for intraocular lenses.

Our FDA research focused on the issue of toxic anterior segment syndrome or TASS. TASS is an acute sterile inflammation occurring within 24 to 48 hours of anterior segment surgery. It is most often associated with cataract surgery. The purpose of our research was to assess intraocular inflammatory potential of the ophthalmic device contaminants identified in the ophthalmic literature as potential causes of TASS. As a result of this research, we also meant to develop and validate appropriate test methods to determine task-related ophthalmic device contaminant levels.

The conclusions of our research are shown on this slide.

Testing a number of different contaminants noted in the literature resulted, and noting a number of contaminants that are not associated with inflammation, our research shows that enzymatic detergents, ethylene oxide, and OVD breakdown products and proteins were not associated with TASS-related inflammation. However, there were a number of contaminants which we did identify as having a significant role in causing anterior chamber inflammation. These include endotoxins, nucleic acids, and metal particles.

As part of this research, we developed a number of testing methodologies, specifically, to detect as -- endotoxin level test method for OVDs to detect the endotoxin levels. In addition, we developed an intracameral injection method for the assessment of intraocular inflammation from specific contaminants.

The results of our research resulted in a number of publications in ophthalmology which are listed here, and they were published online in 2012.

And now Dr. Denise Hampton will present the updates for CLRD.

DR. HAMPTON: Good morning. Good morning to the Panel and to our audience members. My name is Denise Hampton, and I'm the Acting Branch Chief of the Contact Lenses and Retinal Devices Branch, or CLRD.

As noted earlier by Dr. Eydelman, CLRD was the fourth branch created after the reorganization. The staff that comprise our branch are shown on this slide.

The next slide shows the device types that are reviewed within CLRD and include, for example, contact lenses, contact lens accessories, such as care products and cases, rigid gas permeable lenses, or RGP lenses, and retinal prostheses.

Since our last division update at the July 2010 Panel, we granted one de novo petition and approved one humanitarian device exemption, or HDE. The information for these applications follows.

K093937 for the LipiFlow Thermal Pulsation System from TearScience, which is intended for the application of localized heat therapy in adult patients with chronic cystic conditions of the eyelids, including meibomian gland dysfunction, or MGD, also known as evaporative dry eye or lipid deficiency dry eye.

And H110002 for the Argus II Retinal Prosthesis System from Second Sight. This device is indicated for use in patients with severe, profound retinitis pigmentosa who meet the following criteria: Adults age 25 years or older, bare light or no light perception in both eyes; if the patient has no residual light perception, then evidence of intact interlayer function must be confirmed. Continuing on the next slide: Previous history of useful form vision, aphakic or pseudophakic; if the patient is phakic prior to implant, the

natural lens will be removed during the implant procedure; and patients who are willing and able to receive the recommended post-implant clinical follow-up device fitting and visual rehabilitation.

Our branch is active in several ophthalmic device initiatives aimed at expediting innovation of ophthalmic devices. For example, our work on national and international standards and recognition of them, as well as publication of new and revision to existing guidance documents, can lead to improving clinical trials.

In addition, we undertook a series of research experiments to assess safety and performance of contact lenses and care product solutions.

The next two slides show the national, or ANSI, and international, or ISO, standards for contact lenses and care products that FDA recognized since our last division update. As you can see, CLRD staff is very involved in the development and recognition of these standards.

In addition, in March of this year, we published a final guidance document for retinal prostheses, the title of which is shown on this slide.

In an effort to improve regulatory science, we undertook a series of experiments in efforts to better understand the interaction of contact lenses and care product solutions and the implications of that interaction.

Shown on this slide were the goals of our research: To categorize the numerous silicone hydrogel contact lenses in order to address

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concerns with dimensional stability and toxicity; to evaluate the efficacy of care product solutions and contact lenses by conducting a preservative depletion and efficacy study; and lastly, to develop a test method to evaluate disinfection efficacy against acanthamoeba.

The conclusions derived from our research are shown on this slide. Of note, we have developed a subclassification system of silicone hydrogel contact lenses for solution testing. We developed real-world testing of solutions in the presence of lenses by assessing uptake and antimicrobial efficacy. And, lastly, we recommend that acanthamoeba testing be added to the microbe panel for disinfection efficacy testing, and we've developed specific parameters for that test method.

The results of our research were recently published in a November 2012 issue of *Eye and Contact Lens*, and the references are shown on this slide.

Thank you.

MR. CUNNINGHAM: Good morning. My name is Brad Cunningham, Branch Chief of Diagnostic and Surgical Devices, DSDB.

Shown here are some of the folks who were introduced earlier who were new members of our division, and we also have one addition since the last reorg in November of 2012.

This list comprises many of the important devices that we review in our branch. We handle lasers, from excimer lasers for refraction

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procedures and femtosecond lasers, imaging devices, including optical coherence tomography, retinal cameras and scanning laser ophthalmoscopes, tonometers, slit-lamp biomicroscopes, ultrasound biometers, and phacofragmentation systems. However, this list is not exhaustive.

Regarding notable PMA approvals since July 2010, the MEL 80 Excimer Laser System marketed by Carl Zeiss Meditec was originally approved in August 2006 for use in LASIK for the reduction or elimination of myopia up to -7 diopters with or without astigmatism up to 3 diopters. In this recent approval shown on the slide in March 2011, the MEL 80 Excimer Laser System was approved for use in LASIK for the reduction or elimination of hyperopia of less than or equal to 5 diopters with or without refractive astigmatism from greater than .50 diopters up to 3 diopters, with a maximum MRSE of 5 diopters. Additional information about this approval can be found at the website on the slide.

For 510(k) applications, the marketing pathway appropriate, typically, for Class II devices, we have had notable clearances since 2010 for femtosecond lasers used in anterior segment surgery. Specifically, four different companies have been cleared for marketing femtosecond lasers for uses such as anterior capsulotomy, laser phacofragmentation, single and multi-plane corneal cuts/incisions, and single and multi-plane arcuate cuts and incisions in the cornea.

The links to each individual file and additional information can

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be found at these particular web links.

And, lastly, the standards listed on this slide are those that are relevant to our branch and have been recognized by FDA since 2010. It is important to note that our staff are actively involved with the development and recognition of these particular standards. Thank you.

DR. EYDELMAN: Thank you very much. This concludes our division update.

DR. HIGGINBOTHAM: Thank you, Dr. Eydelman, Dr. Kiang, Dr. Hampton, and Mr. Cunningham for those presentations. And a warm welcome to the new members of your team, Dr. Eydelman, and thank you for providing the biographical updates. Thank you.

We will now proceed to the Sponsor's presentation. I would like the Sponsor to approach the podium. I will remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

The Sponsor may now begin your presentation. You have 85 minutes.

MS. McEACHERN: Good morning. My name is Denise McEachern. I'm Vice President of Global Regulatory Affairs for Bausch & Lomb. We are honored and privileged to be here today to present to you, the Ophthalmic Devices Advisory Panel and FDA, the data from PMA P030002

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Supplement 27, demonstrating that the Trulign Toric Accommodating Intraocular Lens provides a safe and effective option for Crystalens patients presenting with significant corneal astigmatism.

More than three million cataract surgeries are conducted annually in the United States. Approximately 25% of patients present with 1.25 diopters or more of corneal astigmatism. The current postoperative goal for surgeons is to leave patients with less than or equal to .50 diopters of residual astigmatism.

Since the current Crystalens models do not have toric correction, the Trulign Toric IOL was designed to meet the needs of Crystalens patients who have at least 0.83 diopters of predicted postoperative corneal astigmatism.

The Trulign Toric IOL was developed as an option for the safe and effective visual correction of aphakia and postoperative refractive astigmatism. It is a biconvex silicone lens with axis marks on the anterior surface and toric correction on the posterior surface. There are no differences to the material or dimensions as compared with the parent Crystalens IOL.

We will present today the established profile of the parent Crystalens Accommodating Intraocular Lens, the need for a safe and effective option for patients with significant corneal astigmatism, and an overview of the design and results of the pivotal clinical trial, Study 650, demonstrating

that the Trulign Toric Intraocular Lens provided correction of refractive astigmatism and, when compared with the Crystalens parent IOL, improved uncorrected distance vision, with no compromise to intermediate or near vision and no introduction of any new safety or effectiveness concerns.

The parent lens for the Trulign Toric IOL is the current Crystalens Accommodating IOL. Crystalens was first implanted in the United States in 2000. The Ophthalmic Devices Advisory Panel reviewed PMA P030002 on May 23rd, 2003, and recommended approved for the Crystalens AT45 IOL. Subsequently, on November 14th, 2003, FDA granted approval of the PMA for the Crystalens Accommodating IOL, Model AT45.

Since the PMA approval in 2003, five supplements with new models have been approved by FDA. All supplements were approved with the indication that I will review shortly, including "provides approximately one diopter of monocular accommodation." Four supplements were approved between 2005 and 2011 with no additional clinical data required and one supplement, Supplement 14, for the HD IOL models, required clinical confirmation. It was approved in June of 2008.

The clinical testing required for approval established the effectiveness of the added indication for the HD model, confirmed that safety and performance was not impacted when compared to the parent Crystalens IOL, and provided confirmation of objective accommodative amplitude. Of note, all but Supplement 20 were approved prior to the approval of the

Trulign Toric IDE, and Supplement 20 was approved well after the approval and initiation of the Trulign Toric clinical trial.

Since approval of the original Crystalens IOL, six additional models have been introduced into the market, and Crystalens IOLs are approved in 69 countries around the world. With over 10 years of clinical experience with this lens, representing implantation of more than 315,000 intraocular lenses, the risk/benefit profile of the Crystalens platform has been well established and is well understood.

The key design features of the Crystalens IOL include a 5.0 optic body, a biconvex shape, rectangular hinged haptics with polyimide loops. These loops help to stabilize the lens within the capsular bag and have indicators to remind the surgeon that it is round to the right, helping to ensure proper positioning of the IOL.

The AT50SE and the AT52SE IOLs have identical optics and haptics, and they differ only by raising each polyimide loop by 0.25 mm to provide two overall diameters, 11.5 mm for the 50 and 12.0 mm for the 52. There is also a 360-degree continuous posterior square edge designed to minimize posterior capsular opacification, or PCO. The power range for the Crystalens products are +4 to +33 diopters.

The approved indication for the AT50SE and the AT52SE IOLs, the parent platform for the Trulign Toric IOL, is shown on this slide. The Crystalens Accommodating Intraocular Lens is intended for the primary

implantation in the capsular bag of the eye for the visual correction of aphakia secondary to removal of a cataractous lens in adult patients with or without presbyopia. It provides approximately one diopter of monocular accommodation which allows for near, intermediate, and distance vision without spectacles.

As stated, the Trulign Toric was designed to perform the same as the non-toric Crystalens IOLs with the exception of the correction of astigmatism. Therefore, with the exception of the words highlighted here in red, which address the astigmatic correction provided by the Trulign Toric IOL, the proposed indication for the Trulign Toric is identical to the indication that was previously approved for the parent Crystalens AT50SE and AT52SE IOLs.

You will recall that the only differences between the Crystalens parent and the Trulign Toric IOLs are the axis marks on the anterior surface and the toric optic on the posterior surface. There are no changes to the product material or the dimensions.

Since the safety and performance of the parent IOL was established and approved in the PMA for the Crystalens IOL, Bausch & Lomb worked with FDA on the clinical study design supporting the modification to add the astigmatic correction. There are no recognized standards or guidances for the study design specifically related to toric IOLs or accommodating IOLs, so utilizing guidance and standards for monofocal IOLs,

for example, the ISO 11979-7 standard, Pivotal Study 650 was designed as a Level B-like study with assistance from FDA.

Study 650 was designed to assess a toric optic's ability to correct astigmatism with no adverse impact on the safety or effectiveness when compared to the established parent Crystalens IOL. The IDE with protocol 650 was submitted to FDA on March 22nd, 2010 and approved on April 23rd, 2010. The PMA supplement was submitted on March 8th, 2012, with clinical data submitted in this PMA for all patients with available data as of database lock on January 25th, 2012.

Representing Bausch & Lomb and the Trulign Toric Accommodating Intraocular Lens are Dr. Jay Pepose, a long-time user of the Crystalens IOL and medical monitor for Study 650. He will provide an overview of the current clinical landscape and the design and conduct of Study 650. Dr. Pepose leads the Pepose Vision Institute and is on staff at Washington University School of Medicine.

Dr. Richard Hope, from Bausch & Lomb, will present the safety results from Study 650, and Dr. Jon Hayashida, from Bausch & Lomb, will provide the effectiveness results from Study 650.

Dr. Adrian Glasser, who is a technical expert in the field of accommodation, will present the evidence for accommodation. Dr. Glasser is Professor of Optometry and Vision Sciences and Biomedical Engineering at the College of Optometry, University of Houston.

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Finally, Dr. Mark Packer, one of the original Crystalens IOL investigators, with over a decade of experience with the Crystalens IOL, will close with a clinical perspective on the Trulign Toric IOL. Dr. Packer is on staff at Oregon Health and Science University.

So with that, I would like to introduce Dr. Jay Pepose.

DR. PEPOSE: Thank you, Denise.

Good morning. I'm Dr. Jay Pepose, and I'm the medical monitor for the Trulign Toric Accommodating Intraocular pivotal study. And for disclosure, I am a paid consultant to the Sponsor, and I have no financial interest in the outcome of today's meeting.

I'm very excited about the Trulign Toric Accommodating Intraocular Lens because it is the first product that addresses two important unmet clinical needs of cataract patients in a single procedure. One, the visual impact of residual uncorrected astigmatism and, two, the desire to have excellent intermediate and functional near vision.

This slide shows the distribution of corneal astigmatism in 6,000 cataract patients prior to surgery. The results are consistent with numerous studies in various cataract populations worldwide that show that between 36 and 39% have over 1 diopter and between 15 and 22% have over 1.50 diopters of preexisting corneal astigmatism.

The importance of surgically addressing corneal astigmatism is seen in this slide, which shows the impact of residual refractive astigmatism

on vision at different vergences. In this study, visual acuity at various focal points was taken in patients with a non-accommodating monofocal IOL first with their best distance correction and then with adding increasing amounts of against-the-rule astigmatism. You can see the detrimental effect of uncorrected residual refractive astigmatism on distance vision. It has less impact on intermediate vision and actually enhances near vision at the cost of blurry distance. With-the-rule astigmatism blurs vision at all vergences. So the need to correct the effect of preexisting corneal astigmatism is paramount if we are to meet our patients' expectation of obtaining excellent uncorrected distance and intermediate vision with functional near vision.

The most common surgical treatment options for corneal astigmatism in cataract patients include astigmatic keratotomy, limbal relaxing incisions, various forms of excimer laser vision correction and toric IOLs.

An obvious advantage of a toric IOL is that it addresses aphakia and astigmatism in a single procedure. Toric IOLs mitigate some of the disadvantages and potential side effects of incisional astigmatic correction, such as variable corneal wound healing and biomechanics, corneal denervation, which may exacerbate dry eye in the older cataract population who are already at higher risk, corneal perforation, infection, wound gape, and decreased best spectacle corrected vision resulting from irregular astigmatism.

The key essential element, the secret sauce, so to speak, of an effective toric IOL is its rotational stability. This is because every degree of misalignment of a toric IOL results in a 3.3% reduction in offset of astigmatism. That means that for a 10-degree misalignment, the toric effect is reduced by a third. In subsequent presentations, you will see that 96.9% of the Trulign Toric IOLs had less than or equal to 5 degrees of rotation between the day of surgery and four to six months postoperatively. No eye had greater than 10 degrees of rotation. And the mean rotation was between 1.35 and 1.78 degrees for the three Trulign Toric powers evaluated. In summary, the Trulign Toric Accommodating IOL demonstrates exquisite rotational stability.

I began this presentation by emphasizing that the Trulign Toric Accommodating IOL addresses two important unmet clinical needs, one of which is offsetting substantial preexisting corneal astigmatism, which impacts over 1 in 3 patients. The other desire that patients express is the ability to have excellent uncorrected distance and intermediate vision with functional near vision. Patients want to be able to drive easily at night, use one of the ever-expanding handheld device options, check e-mail on their smartphone, shave, put on makeup, and check out their Facebook page on the computer. Many patients don't mind the use of reading glasses for sustained reading, particularly in low lighting, but want to have great intermediate vision and be able to see who is calling on their cell phone without having to fumble for

reading glasses.

In general, monofocal non-accommodating intraocular lenses do not address the intermediate and near needs of patients and leave them dependent on glasses for these tasks. This slide shows the defocused curve of the Alcon AcrySof SN60WF Monofocal Non-Accommodating IOL. Note the vision at distance, intermediate, and near object distances. Here are the results with the CeeOn 911A Non-Accommodating Monofocal IOL at distance, intermediate, and near.

In comparison, here are the mean distance-corrected visual acuities at distance, intermediate, and near with the Trulign Toric Accommodating IOL. All of the data for all of the IOLs on this slide are visual acuity obtained through the patient's distance correction. This obviates the effect of any residual refractive error and demonstrates the true inherent performance of each IOL as if each patient achieved a perfect plane of refractive outcome. You can see that the improvement at intermediate and near vision with the accommodating IOL is in marked contrast to the standard non-accommodating IOLs. This is also evidenced by the lower 1.43 diopter required near spectacle add for the Trulign Toric Accommodating IOL in comparison to the 2.5 diopter required near spectacle add for the non-accommodating monofocals, which is consistent with approximately one diopter of accommodation.

The approved toric IOL options are limited and do not address

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the intermediate and near vision demands of cataract patients with active lifestyles. The STAAR Elastic Toric is available in only two cylindrical powers and is a monofocal non-accommodating IOL. The Alcon AcrySof Toric is also a non-accommodating IOL. The data from Pivotal Study 650 demonstrate how the Trulign Toric Accommodating IOL addresses both the effect of preexisting corneal astigmatism in cataract patients and also provides excellent uncorrected distance and intermediate vision, with functional uncorrected near vision.

As medical monitor of Study 650, I would now like to provide an overview of the design and conduct of this pivotal clinical trial. Study 650 was a prospective, randomized, multicenter, single-masked clinical trial performed to evaluate the safety and effectiveness of the Trulign Toric Accommodating IOL. As mentioned earlier, the safety and effectiveness of the parent lens, the Crystalens Accommodating IOL, was previously demonstrated.

Study 650 utilized standard inclusion and exclusion criteria typical of an IOL study in cataract patients. The key inclusion and exclusion criteria pertinent to evaluating a toric IOL are listed here.

Those subjects who met the eligibility requirements were enrolled in Study 650. The primary effectiveness endpoint was to demonstrate a statistically significant superiority of the lowest toric power, 1.25 diopters, over a spherical control for the percent reduction of cylinder.

Therefore, to adequately power the study, the largest enrollment was required in the control and toric 1.25 dioptic groups.

Those subjects who qualified for the lowest astigmatic cylinder range were randomized in a 1:1 ratio between the spherical control and the toric 1.25 diopter IOL with a minimum enrollment of 72 subjects per group. Those subjects with higher cylinder ranges were enrolled in either the toric 2 diopter or toric 2.75 dioptic groups, with a minimum combined enrollment of 56 subjects and a minimum of 10 subjects enrolled in the highest toric group.

The examination schedule and follow-up visits are listed here. On the day of surgery, eligibility was confirmed and randomization occurred between the control and toric 1.25 dioptic cohorts. At the Form 4, or four- to six-month visit, rotational stability was established, and the safety and effectiveness endpoints were evaluated.

At the preoperative visit, a vector analysis was performed to determine eligibility for enrollment. A toric calculator was used to determine the predicted postoperative corneal astigmatism utilizing a fixed SIA, or surgically induced astigmatism, of .50 diopters.

On the day of surgery, subjects were unilaterally implanted. Therefore, it is important to note that, for this reason, no binocular acuity assessments or evaluation of spectacle independence were performed in Study 650. The primary cataract incision was performed on the steep axis because this is one of the preferred practice patterns of Crystalens surgeons,

as a method of reducing corneal astigmatism and to minimize study variability.

At the operative and postoperative visits, lens axis misalignment and rotational stability were evaluated with digital slit-lamp photography using iris and conjunctival landmarks as reference points. Assessment was performed by an independent reading center utilizing a validated image analysis technique with repeatability of plus or minus 0.79 degrees. Additionally, a questionnaire was administered to evaluate the subjective elements of the study, and of primary interest with the induction of significant visual disturbances in subjects implanted with the Trulign Toric IOL.

The statistical analysis plan, or SAP, was initially provided to and approved by the FDA in the original study protocol. Two interim analyses using unaudited, unlocked, partial data were performed. The first interim analysis was performed early on, with 35 of the 229 subjects available for analysis at Form 4. This analysis was performed for planning purposes for other potential toric clinical trials. The second interim analysis used the unaudited partial data at the Form 3 visit, not the Form 4 effectiveness endpoint, to simulate the format and presentation of the clinical data.

Although interim analyses were conducted prior to finalization of the SAP, they occurred after all patients had been enrolled. They did not affect the sample size or patient selection, and the safety and effectiveness

endpoints and methods of analysis were unchanged. The study was sufficiently powered in that making an alpha adjustment for performing these two analyses would not impact either the conclusions of the study for effectiveness or the overall statistical significance.

Bausch & Lomb subsequently produced a SAP as a separate document to provide additional detail on the planned analyses originally presented in the study protocol. The SAP was amended to provide further clarification of the analysis and to ensure alignment with the required ISO and ANSI standards for toric IOLs. These included clarification of the definition for best use, revision of the definition of persistent AEs per ANSI guidance, and removal of vector analysis for lens misalignment based on manifest refraction, with FDA agreement. Importantly, the SAP was amended prior to the primary analysis for PMA submission.

FDA has raised a concern regarding these two unplanned interim analyses and amended statistical analysis plan for Study 650. The information that I have shared should allay any concerns in that: (1) these interim analyses did not affect the original planned analyses for the study; (2) neither the conduct of the study nor the SAP was revised in response to either of these analyses; and (3) the study was sufficiently powered so that the conclusions and overall significance would not be altered by making an alpha adjustment for these two looks at the partial interim data. A Bonferroni adjustment for these interim analyses would still result in a

p-value of less than 0.001.

Bausch & Lomb reported 391 total deviations in Study 650, which consisted of 14 major deviations in 12 eyes and 377 minor deviations. Four of the minor deviations were reclassified as major during the review of the submission through Amendment 4. Additionally, the FDA considered implantation of the 10 AT52 lenses, which differ from the AT50 lenses only by a 0.25 mm extension of each pair of polyimide loops, as major deviations.

241 of these 401 deviations, a full 60%, occurred preoperatively while the patient still had a cataract. Examples include failure to record intermediate vision or pupil diameters preoperatively, long before implantation of the study or control device. Obviously, these preoperative deviations had no impact on subsequent efficacy determinations between the toric and control IOLs.

Based upon thorough review and analysis of all protocol deviations, I can report with confidence that these did not impact either the scientific integrity of the data or the statistical and clinical validity of the conclusions.

As you can see, none of the major protocol deviations impacted the Form 4 visit, which was the visit at which the safety and effectiveness endpoints were assessed. As for the 29 minor protocol deviations which occurred at the Form 4 visit, they were procedural in nature and had no impact on the safety and/or effectiveness endpoints.

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As you can see here, inclusion or exclusion of the 10 AT52 implanted lenses had no effect on the overall effectiveness outcomes of the study. Therefore, Bausch & Lomb pooled the results of the AT50 and the AT52 lenses.

Statistical analysis and conservative imputation were performed to assess the impact of protocol deviations, including implantation of the AT52 lenses, on the primary effectiveness outcome. As you can see, the removal or inclusion of protocol deviations using conservative imputation does not change the conclusion of the primary effectiveness outcome.

All protocol deviations were included in the safety cohort to ensure that all safety events were assessed. As outlined in this summary, a detailed and thorough review and analysis of all protocol deviations demonstrates the integrity of the data and supports the scientific, statistical, and clinical validity of the conclusions.

As I conclude my comments, I would like to put these results into a broader perspective. The critical requirements of an effective toric IOL are that it exhibits effective correction of refractive astigmatism, as demonstrated by minimal residual refractive cylinder, demonstrates excellent rotational stability, and resides on a platform which provides outstanding refractive predictability as demonstrated by high accuracy to target for manifest refraction spherical equivalent, or MRSE. If the above criteria are achieved, they should yield the desired goal of good uncorrected distance

visual acuity.

The effectiveness data from Study 650 demonstrate that the Trulign Toric Accommodating IOL corrects refractive astigmatism and provides distance, intermediate, and functional near vision in a single procedure. There was an 85.8% reduction in refractive cylinder in the all-toric group, and the toric 1.25 dioptic group was statistically superior to the spherical control. As evidence of its outstanding refractive targeting predictability, nearly 80% of the all-toric group were within .50 diopters of intended.

The data also demonstrate that the Trulign Toric Accommodating IOL has superb rotational stability in the early postoperative period, with less than 2 degrees of IOL rotation reported between the day of surgery and four to six months postop. Additionally, 96.9% of eyes exhibited less than or equal to 5 degrees of rotation over that same time interval. This resulted in a statistically significant improvement in uncorrected distance visual acuity over the spherical control, with a mean uncorrected distance vision of 20/25 and exceptional uncorrected intermediate vision of 20/20, with functional near vision as well. As shown earlier, these visions at intermediate and near are nearly double those reported in studies of non-accommodating monofocal IOLs.

Thank you for your attention, and I would now like to introduce Dr. Richard Hope.

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DR. HOPE: Thank you, Dr. Pepose.

Good morning. My name is Richard Hope, and I am a medical director at Bausch & Lomb. I'm going to be speaking today about the safety outcomes from the Trulign 650 study.

I'd like to start by pointing out that the safety profile of the parent Crystalens has been well established. As you heard from Ms. McEachern, Crystalens was approved by FDA in 2003. So we have nearly 10 years of experience in the real-world setting, with more than 315,000 eyes implanted. Bausch & Lomb has carefully reviewed this large body of postmarket surveillance data, and we know that the global incidence rate for adverse events has been quite low, right around 1%.

Now, onto the data for the Trulign Toric IOL. The primary safety endpoints for the 650 study were preservation of best corrected distance vision at Form 4 compared to the ISO grid, preservation of best corrected near vision at Form 4, and incidence of cumulative adverse events compared to the ISO grid. And as you will see, Trulign met all of the safety endpoints.

The data from the following slides are based on the safety cohort. This cohort includes all subjects implanted with either the control or toric lenses. 229 subjects were initially enrolled minus 2 subjects that were not implanted. So the safety cohort consists of 227 subjects, with 76 in the control group and 151 in the toric group. Because several of the safety

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outcomes are specific to the Form 4 visit, please note that only 69 control eyes and 142 all toric eyes reached Form 4 as of the database log on January 25th, 2012.

Best corrected distance vision outcomes for the safety cohort exceeded the grid from ISO standard 11979. You can see that 100% of the subjects in the control group and 97.9% of subjects in the all toric group had best corrected distance vision of 20/40 or better at Form 4. So both groups exceeded the ISO grid level of 92.5%.

Best corrected near vision was even better, with 100% of subjects in both the control and all toric group reaching a best corrected near vision of 20/40 or better at Form 4. And again these outcomes exceeded the ISO grid level of 92.5%.

Surgical adverse events in the 650 study were common issues that are typical for cataract surgery. The rates were low and comparable between the two groups. In the control group, three adverse events occurred in two subjects: one corneal abrasion and two radial tears of the anterior capsule during capsulotomy. In the all toric group, there were five adverse events, a sty that was discovered on the operative day, a complaint of foreign body sensation several hours after surgery, a corneal incision made on the incorrect axis, and an iris injury and a posterior capsule rupture, both of which occurred intraoperatively.

All of these adverse events were assessed as unrelated to the

study device and were not unique to any IOL design or model, and all seven subjects reached 20/25 or better best corrected vision at the Form 4 visit.

Postoperative ocular adverse events were also the types of issues that are common and typical for patients in this age group undergoing cataract surgery. The most frequently reported events were dry eye, followed by blepharitis, punctate keratitis, and posterior vitreous detachment.

Cumulative adverse events in the 650 study were below the grid level for all categories per ISO standard 11979. In fact, there were only two events: one case of macular edema, which resolved by Form 4 and improved to 20/25 best corrected vision; and one case of secondary surgical intervention, which was a repositioning of the lens, and that patient improved to 20/32 best corrected vision.

So, in summary, the incidence rate for adverse events for the Trulign Toric IOL was below the safety and performance endpoint for all categories in the ISO grid.

With regards to ocular serious adverse events, one case occurred in the control group. The event was a malposition of the intraocular lens, where the inferior haptic was placed in the sulcus and the superior haptic was placed in the capsular bag. This was noticed on the first postoperative day. A secondary surgical procedure was performed to reposition the inferior haptic into the capsular bag. The patient had a good

outcome, with a best corrected vision of 20/32 at the Form 4 visit. This type of event is due to error and surgical technique and could have occurred with any model IOL. Now, the direction for use, or DFU, for Crystalens does instruct surgeons to rotate the lens at least 90 degrees after implantation to help confirm that both haptics are in the bag.

One serious adverse event occurred in the toric group. This was an anterior vault which was observed at the Form 4 visit 124 days after the initial surgery. Approximately 2 diopters of myopic shift was present compared to Form 3, but there was no change in astigmatism. The IOL was repositioned using viscodissection. No attempt was made to realign the IOL to the correct axis due to regional fibrosis of the capsule and the surgeon's medical judgment. The vault resolved, and the patient regained best corrected vision of 20/32 with residual astigmatism due to lens axis misalignment.

In this case, the surgeon reported that the patient was noncompliant with postoperative anti-inflammatory medications and developed early signs of capsular striae post-implantation in both eyes. The surgeon did not perform the eye capsulotomy on the study eye, which subsequently developed vault. The surgeon did perform YAG on the fellow eye and vault did not occur.

The DFU for Crystalens recommends that patients be kept on anti-inflammatory medications for at least four weeks, and published

literature support the use of YAG capsulotomy in response to capsular fibrosis to prevent or treat vault.

Additionally, one ocular serious adverse event occurred in a non-study fellow eye, which was implanted with a different model of Crystalens. The event was an asymmetric vault which was observed at the Form 4 visit, 132 days after implantation. The original Crystalens was exchanged for a second Crystalens, which vaulted intraoperatively, so a monofocal IOL was placed in the sulcus. After the IOL exchanged, most of the astigmatism resolved and MRSE approached plano. The patient eventually regained uncorrected and best corrected vision of 20/32 after resolution of corneal edema.

In this case, two potential risk factors were present: residual cortical material and zonular dehiscence. Please note that the DFU for Crystalens recommend meticulous cortical cleanup and warns against implantation in the presence of zonular rupture.

The level of significant PCO at the Form 3 and Form 4 visits was low and similar between the two groups. The eye capsulotomy rate was around 18% in the control group and 6.6% for the all toric group. Nearly all of these lasers were performed beyond four months postop. And no serious adverse events were reported in association with the lasers.

So, in summary, all of the safety endpoints were met, including preservation of best corrected vision at distance and near, with both

exceeding that of the ISO grid level in the incidence of adverse events which were below the levels of the ISO grid. Serious adverse events were rare, and all three patients reached best corrected vision of 20/40 or better at their final visits. No new safety concerns were introduced with the addition of the toric optic for Trulign compared with the approved parent Crystalens, and no secondary surgical interventions were performed to address rotational stability.

So, in conclusion, the safety outcomes for the 650 study demonstrate that the Trulign Toric Accommodating Lens is safe for intended use.

Thank you for your time. It is my pleasure to introduce our next speaker, Dr. Jon Hayashida.

DR. HAYASHIDA: Thank you, Dr. Hope.

Good morning. I am Jon Hayashida. I serve as the Vice President of Clinical and Medical Affairs at Bausch & Lomb Surgical. It is my pleasure to present to you the effectiveness results from Pivotal Study 650, which evaluated the Trulign Toric Accommodating IOL.

Here are the primary, secondary, and other effectiveness endpoints for Study 650. As you can see, there is a combination of endpoints which assess the effectiveness of a toric IOL and others that assess the effectiveness of a lens which provides distance, intermediate, and near vision.

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This slide summarizes the effectiveness outcomes. The primary effectiveness endpoint was achieved by statistically significant superiority of the 1.25 diopter toric IOL over the spherical control IOL for percent reduction of cylinder, with a p-value of less than .001. The all toric cohort reported a mean of 85.8% reduction of cylinder and a mean of less than .50 diopters of residual cylinder for the 1.25, 2, and 2.75 diopter toric IOLs.

Rotational stability was also demonstrated, with a mean axis misalignment between the day of surgery and a four- to six-month postop visit of less than 5 degrees and rotational stability of less than 2 degrees over that same interval, resulting in a mean uncorrected distance visual acuity of 20/25, with no significant visual disturbances.

Here are the demographics for the pivotal Trulign Toric study. The mean age for the spherical control cohort was 69.8 years while the mean age for the all toric cohort was 70.1 years. There were slightly more females than males who participated in the study. The p-values on the right demonstrate that there are no significant differences between the control, the 1.25 diopter or all toric cohorts. Additionally, the ethnicity distribution was 85.5% Caucasian, 3.1% each for Hispanic and Asian, and 1.8% African-American.

At the time of the database lock on January 25th, 2012, there were a total of 229 subjects enrolled in Study 650. The effectiveness cohort consists of the 229 subjects in the all enrolled cohort minus two subjects who

were not implanted with a study IOL and 12 additional subjects who were removed due to 14 major protocol deviations. This results in a total of 215 subjects in the effectiveness cohort.

At the time of database lock, 16 of the 25 subjects had not yet completed Form 4 or the four- to six-month follow-up visit. This results in 199 subjects, 66 control, 133 all toric, who had Form 4 effectiveness data reported.

Let's look at the performance of the Trulign Toric Accommodating IOL. The 1.25 diopter toric IOL reported an 81% reduction in absolute cylinder, and this represents statistically significant superiority over the subjects with similar corneal astigmatism implanted with a spherical control IOL with a p-value of less than 0.001, meeting the primary effectiveness endpoint.

Let's look at another effectiveness outcome further supporting the superiority. In this graph, you can see a comparison between the spherical control and the 1.25 diopter toric IOL with regards to absolute residual cylinder. As you can see, statistically significant superiority of the 1.25 diopter toric IOL over the spherical control was demonstrated as well.

The percentage of eyes within .50 and 1 diopter of the intended correction of refractive cylinder is represented on this slide. Again, the superiority of the toric cohort over the spherical control cohort is demonstrated with 79.7% of eyes within .50 diopters of intended correction

and 95.5% of eyes within 1 diopter of intended correction.

As you have seen, the Trulign Toric IOL has demonstrated good correction of refractive astigmatism. Another example of demonstrating effectiveness is to compare the magnitude of corneal cylinder at the four- to six-month postoperative visit with the magnitude of residual refractive cylinder at that same visit. As you can see, eyes qualifying for the lowest toric cohort were randomized 1:1 between the spherical control and the 1.25 diopter toric IOL. Therefore, their corneal cylinders are the same, as depicted there in green.

However, consistent with the previous slides, the superiority of the toric IOL is demonstrated. For eyes implanted with the 2 diopter and 2.75 diopter toric IOLs, equivalent higher corneal astigmatism is demonstrated. What is impressive is that all toric IOLs had a mean residual refractive astigmatism of less than .50 diopters.

Rotational stability was assessed for all subjects in the all toric cohort. As Dr. Pepose stated, this assessment was performed utilizing digital slit-lamp photography at an independent reading center. Unfortunately, there were times when photos were determined to be unusable due to poor illumination or shadows. This resulted in a very small number of eyes which were removed from analyses. Specifically, four eyes from the lens axis misalignment and six eyes from the absolute rotation assessment were removed.

For rotational stability between consecutive visits, this assessment utilized the consistent cohort which required that subjects provide data at both the Form 3, one- to two-month, and Form 4, four- to six-month, visits. This resulted in a total of 121 subjects who provided data meeting this criteria for the consistent cohort.

This table shows the lens axis misalignment between the preoperative target axis as determined by the toric calculator and the toric lens axis orientation at four to six months postop.

To put this in perspective, the resultant lens axis misalignment has three contributing factors. The first is accuracy of marking the steep axis prior to surgery. The second is accuracy of toric IOL orientation at the time of surgery. And, third, toric IOL rotational stability. For the Trulign Toric Accommodating IOL, the mean lens axis misalignment was reported to be less than 5 degrees.

Therefore, of the three contributing factors for lens axis misalignment, if we look at just the toric IOL rotation from the day of surgery to four- to six-month postoperative, the mean toric IOL rotation was reported to be less than 2 degrees. An impressive 96.9% of eyes exhibited less than or equal to 5 degrees of IOL rotation.

A benchmark for toric IOL rotational stability is provided by the ANSI guidance. Per this guidance, stability of the toric IOL axis is achieved when 90% of implanted lenses rotate less than or equal to 5 degrees

between two consecutive visits at least three months apart. In the consistent cohort, 99.2% of all Trulign Toric IOLs demonstrated less than or equal to 5 degrees of rotation between visits.

To achieve good uncorrected visual acuity, it is important to not only have minimal residual refractive astigmatism but good accuracy to target for manifest refraction spherical equivalent or MRSE. The Trulign Toric Accommodating IOL demonstrated an accuracy to target of MRSE of 73.7% within .50 diopters and 93.2% within a diopter. This resulted in a mean uncorrected distance visual acuity of 20/25 at the four- to six-month postoperative visit. Additionally, both the 1.25 diopter toric and all toric cohort demonstrated statistically significant superiority over the spherical control IOL for uncorrected distance visual acuity.

To assure that placing a toric optic on an accommodating platform did not compromise its performance, other effectiveness outcomes were measured and reported. Therefore, measurement of intermediate and near vision through a distance correction eliminates any compromise or benefit from residual refractive error. As you can see, no difference between the spherical control and the all toric IOL cohort was demonstrated. What is noteworthy is the mean residual add of 1.43 diopters for the Trulign Toric IOL. This is consistent for an accommodating IOL providing approximately one diopter of add.

So what was the vision Trulign Toric Accommodating IOL

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experienced monocularly without glasses? As you remember, the mean uncorrected distance visual acuity was 20/25, and the 1.25 diopter toric and all toric cohorts demonstrated statistically significant superiority over the spherical control IOL. The mean uncorrected intermediate vision was 20/22. However, no difference between toric and spherical control cohorts was demonstrated. The mean uncorrected near vision was 20/40, and again, no difference between toric and spherical control cohorts was also demonstrated.

As clinicians, we understand the influence of residual refractive error on visual acuity. In particular, residual myopia can aid in uncorrected intermediate and near vision. Therefore, uncorrected distance, intermediate, and near visual acuity were reanalyzed controlling for MRSE. For uncorrected distance visual acuity, the statistically significant superiority of the toric over the spherical control continues to be demonstrated. For uncorrected intermediate and near visual acuity, there was no difference exhibited between the toric and spherical control accommodating IOLs. However, this is expected since either the residual astigmatism in the spherical control cohort at intermediate or the magnitude of blur induced by the absence of a full reading add at near prohibits the patients from being able to discern a measurable difference.

As reported in this slide, the Trulign Toric Accommodating IOL did not demonstrate any significant lens tilt or decentration.

Placing a toric optic on an accommodating IOL could raise concerns related to the induction of subjective visual disturbances especially in the highest toric power. There was only one subject who reported a significant visual disturbance in the toric cohort. It was determined that this patient had developed moderate posterior capsular opacification, or PCO, and after YAG capsulotomy, the patient reported that the visual disturbances had resolved. With regard to the five subjects in the spherical control cohort, all reported PCO at the Form 4 visit. Three underwent YAG capsulotomy, and all three reported resolution. Two others have not undergone YAG capsulotomy.

So, in conclusion, effectiveness of the Trulign Toric IOL has been demonstrated for the correction of astigmatism. An 85.8% reduction in refractive cylinder was demonstrated for the all toric cohort, and statistically significant superiority of the 1.25 diopter toric IOL over the spherical control IOL was demonstrated. Additionally, 79.9% of eyes were within .50 diopters of the intended refractive cylinder, resulting in the 1.25, 2, and 2.75 diopter toric IOL, each reporting a mean of less than .50 diopters of residual refractive astigmatism postoperatively.

Excellent rotational stability was demonstrated, with a mean of less than 2 degrees of IOL rotation reported between the day of surgery and four- to six-month postoperative visit. An impressive 96.9% of eyes exhibited less than or equal to 5 degrees of IOL rotation over that same time interval.

When comparing the Trulign Toric to a spherical accommodating control IOL, subjects also reported statistically significant superiority in uncorrected distance visual acuity, with no significant visual disturbances reported.

Finally, no compromise in the addition of a toric optic to the parent accommodating IOL platform was observed, as demonstrated by no compromise in distance corrected intermediate and near vision or uncorrected intermediate and near vision, with a mean add of 1.43 diopters.

Overall, the Trulign Toric Accommodating IOL provides an effective correction for postoperative refractive astigmatism, providing the patient with good uncorrected distance and intermediate vision, with functional near vision. Therefore, the Trulign Toric Accommodating IOL is effective for its intended use.

I would now like to invite to the podium Dr. Adrian Glasser.

DR. GLASSER: Thank you, Jon.

Good morning. My name is Dr. Adrian Glasser. I'm a Professor in the College of Optometry at the University of Houston, and my area of expertise is accommodation and presbyopia. In 2003 I assisted the company Eyeonics in gaining FDA approval for the AT45 Crystalens as an accommodating IOL. I am here today in my capacity as a paid consultant to Bausch & Lomb to address the accommodation claim for the Trulign Toric IOL.

In 2003 the original parent lens to the Trulign Toric IOL, namely

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the AT45, received FDA approval with a claim for accommodation. There was at that time no ANSI or ISO standards or other guidance specifying requirements for specific accommodation testing. Nevertheless, the Crystalens AT45 was approved as an accommodating IOL based on the PMA data, which included a comparison between the AT45 and a standard monofocal control IOL.

Subsequent data supporting the accommodation claim of the AT45 includes wavefront measurements and data from a study published by Macsai et al. in 2006. In addition, in 2007, data in support of the AT45 HD-100 Level B modification presented to FDA included A-scan ultrasound measurements of anterior IOL movement with drug-stimulated accommodation. The present PMA Study 650 from 2010 to 2012 also had no specific requirement for accommodation testing, and nor was any requirement expected because of the prior history of approvals of the five supplements to the original AT45 parent lens.

Among the data presented in the 2003 Crystalens AT45 PMA that led to approval as an accommodating lens was the comparison between the Crystalens and a monofocal control IOL. The near add power required to achieve best near visual acuity was determined for both groups. Plus, lenses were added in .25 diopter steps until patients achieved the best possible vision at near.

As can be seen, there is a clear separation in the distribution

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between the two groups. The mean add required for the standard monofocal IOL was 2.32 diopters, whereas the mean add required with the Crystalens was 1.24 diopters. This is a difference in the near add power of 1.12 diopters. This is part of the data that led to the PMA approval, with a claim for approximately one diopter of accommodation.

In addition, also for the AT45 PMA, evidence of accommodation was evaluated in 10 eyes of five subjects at one site. Testing included dynamic retinoscopy, defocused curves, wavefront measurements evaluating near vision through the distance correction before and after cycloplegia, and evaluation of a change in anterior chamber depth with drug-stimulated accommodation. Dynamic retinoscopy demonstrated 3.14 diopters of accommodation. Monocular and binocular defocus showed 2.42 diopters and 2.65 diopters, respectively. Wavefront measurements showed up to 2.93 diopters.

A-scan ultrasound demonstrated forward movement of the optic by 0.65 mm, with drug-stimulated accommodation. This forward movement of the Crystalens would equate to about .8 diopters of accommodation from simple schematic eye calculations.

Thus, again, although there was no specified requirement for accommodation testing, all these tests were performed, and they provided good evidence for accommodation that resulted in the Panel voting for the accommodation claim and FDA approving the accommodation claim in the

AT45, the parent lens to the Trulign Toric IOL.

In addition, wavefront maps from a Crystalens from Dr. Packer's practice show objective measurement of accommodation. The difference in the power maps from distance, at left, to near, at right, show a clear demonstration of a power change consistent with about 1.6 diopters of accommodation. This is from a 63-year-old male at one year postop with a Crystalens AT45.

In addition, objective dynamic accommodation measurements with a COAS wavefront aberrometer in a Crystalens patient shows clear, objective evidence of accommodation from the myopic shift in refraction to a near stimulus.

The published Macsai et al. 2006 study used several different measures of accommodation in 56 Crystalens patients -- that's 112 eyes -- to show significantly better accommodation of the Crystalens compared to a standard monofocal control IOL. As the table shows, from dynamic retinoscopy, monocular and binocular defocus and monocular and binocular near point, the Crystalens outperformed the control IOL, with each measure showing a statistically significant difference. Dr. Packer will mention several other published studies, all of which are consistent with accommodation in the Crystalens patients. This Macsai study does acknowledge in the conclusion that Crystalens perceived a greater accommodative ability than was actually measured. Why this is and what is the best method to measure

the many factors that contribute to accommodation remain subject to debate.

FDA did actually require objective accommodation data to be included in the AT45 HD-100 Level B modification PMA supplement. This included immersion A-scan ultrasound measurements of drug-stimulated accommodative IOL movement in 35 eyes. This was in accordance with the ANSI accommodative IOL draft standard available at the time. Subjectively measured accommodation with MN Read Cards in 33 eyes also included in that submission shows a mean of 3.93 diopters. Based on these data presented to FDA in late 2007, continued approval was granted for labeling as an accommodative IOL.

Shown here is the decrease in anterior chamber depth from the cycloplege state to the drug-stimulated accommodated state in 31 primary eyes, which shows the accommodative forward movement of the Crystalens AT45 HD-100.

Now, to the present PMA for the Trulign Toric IOL. Again, although there was no specified requirement for accommodation testing, data from Pivotal Study 650 are available to support equivalent accommodative performance of the Trulign Toric to the control parent Crystalens. The following two slides will show appropriate comparisons in the data, comparing the Trulign Toric IOL and the control lenses to demonstrate equivalent or better visual performance at distance,

intermediate, and near.

The control lenses used were the parent lenses to the Trulign Toric IOL, namely the Crystalens AT50SE and AT52SE accommodating IOLs.

On the left, the percentage of eyes for uncorrected distance visual acuities for all acuity levels is superior for the Trulign Toric IOL compared to the parent accommodative Crystalens. This is expected from the astigmatism correction achieved by the Trulign Toric IOL. In addition, on the right, the percentage of eyes are essentially equivalent at all acuity levels for distance corrected near visual acuities at 40 cm between the Trulign Toric IOL and the parent Crystalens.

Therefore, since both distance and near visual acuities are comparable, if not better, for the Trulign Toric IOL, this justifies the same accommodation claim for the Trulign Toric IOL as for the parent lens.

Further, uncorrected distance, intermediate, and near visual acuities are comparable and, in fact, better for the Trulign Toric IOL compared to the parent Crystalens IOL. This parent Crystalens received and still today has labeling as an accommodative IOL. Therefore, this data also justifies the same accommodation claim for the Trulign Toric IOL as for the parent lens.

To address the specific concern raised by FDA as to whether the PMA data presented are sufficient to support an accommodation claim for the Trulign Toric IOL, there was no specified requirement for objective or even subjective accommodation testing. Therefore, a monofocal IOL was not

used, which would have -- an explicit assessment of accommodation. There was no expectation of having to support an accommodation claim since all prior Crystalens supplements have been approved with a claim for accommodation.

The data to support the accommodation claim for the Trulign Toric IOL, therefore, remains the same data previously presented to FDA for the parent lenses, which were sufficient to achieve the accommodation claim that remains in place today.

Furthermore, new data from the present study demonstrates that the Trulign Toric performs just as well as the parent Crystalens at distance, intermediate, and near, and therefore, we believe the Trulign Toric IOL should be granted the same accommodation claim and labeling as the parent lens.

Finally, as you saw previously from Dr. Pepose, data from Pivotal Study 650 shows that the Trulign Toric IOL outperforms two other monofocal IOLs at intermediate and near.

In summary, then, we believe that the original data supporting the accommodation claim in the parent lens in conjunction with the additional data shown from Study 650 support comparable accommodative performance of the Trulign Toric IOL to the parent lenses.

Thank you for your attention. I'd now like to introduce  
Dr. Mark Packer.

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DR. PACKER: Thank you very much, Dr. Glasser.

Well, it's a great pleasure to be here this morning, and it's very exciting to present data in support of approval for the Trulign Toric Accommodative Intraocular Lens. I'm a cataract surgeon, and I was one of the original investigators for the AT45 Crystalens IDE. I implanted my first Crystalens almost 13 years ago, in April of 2000, and I'm excited about the addition of the toric optic to this parent accommodative lens.

I am here today as a paid consultant to Bausch & Lomb. However, I have no financial interest in the outcome of today's proceedings.

In considering the data you've heard so far today, you can see that adding a toric optic to this established parent intraocular lens has introduced no new risks. And the current risks of the parent lens are already well known and understood. At the same time, you've seen that there are increased benefits to the toric optic, specifically in terms of the superior uncorrected distance visual acuity. For me, in my practice, I know that this will also mean a reduction in the need for additional enhancement procedures such as corneal relaxing incisions and LASIK for patients who receive accommodative intraocular lenses, because the toric optic will obviate the need for additional procedures to correct residual astigmatism.

The current risks of the parent platform which you've seen described today include anterior and asymmetric vault. We've known about these problems for over a decade and have developed successful mitigation

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and treatment strategies. The benefits are clear, better uncorrected distance vision, great intermediate and functional near vision thanks to the presbyopia correction of the accommodative lens, rotational stability, which leads to excellent correction of astigmatism, and therefore, given these factors, presumed reduced spectacle dependence.

Let's turn first to the risk of anterior and asymmetric vault.

This problem occurs because of the hinged haptic design of this accommodative lens due to the forces of normal capsular contraction that occur with all intraocular lenses. The hinged haptics can cause the lens to buckle as you see here and vault forward or in an asymmetric fashion.

We've developed mitigation strategies to help prevent this problem. You can see here a Crystalens patient that is three years postop, one of my patients, and I can achieve results like this through careful sizing of the capsulorhexis, meticulous cortical cleanup, leaving a pristine capsular with virtually no lens epithelial cells, appropriate IOL positioning and a watertight closure of the corneal incision with a suture, if necessary. In addition, postoperative medical therapy, topical anti-inflammatory agents, and the use of a cycloplegic in the immediate postoperative period can be helpful in preventing capsular contraction and vault.

As we have introduced these strategies, the Sponsor has codified them in the directions for use. All of these mitigation strategies are published and provided to Crystalens surgeons with the devices.

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As these strategies have become known and we've presented them at various meetings, the incidence of vault has declined over time. Now, we know that there is some underreporting with complaints. Clearly, not every episode of vault is reported. But if we assume that the underreporting has been about the same over the last decade, we can still see that the incidence has declined. In addition, if you look at the y-axis here, the top value is not 100%, it's 1%, so the incidence is very low and it's getting lower.

If vault does occur, we do have treatment strategies as well. Early on, if we see capsular striae, we can perform a preemptive capsulotomy with relaxing posterior capsular laser incisions to relieve the stress of the posterior capsule and allow the lens to relax into its appropriate position. Finally, a repositioning or IOL exchange can be performed, and fortunately, in general, patients who undergo these procedures maintain good best corrected visual acuity. Finally, in some cases with minimal vault, it may not be necessary to perform an intraocular procedure. If the vault remains stable, a corneal refractive procedure can eliminate the induced myopia and astigmatism.

The benefits of this new lens stem from a combination of the parent accommodating platform and the introduction of the toric optic. The accommodating lens provides great intermediate and functional near vision, and thanks to its rotational stability, the toric lens provides astigmatism

correction.

Let's look first at the intermediate and near vision. We have seen, and there is published data to support superior uncorrected intermediate and uncorrected near as well as distance corrected intermediate and distance corrected near of the Crystalens platform when compared to monofocal intraocular lenses. In addition, we see superior uncorrected intermediate and distance corrected intermediate vision as well as superior quality of vision when compared to other available presbyopia correcting lenses available in the market today; that is, multifocal IOLs.

There are also objective measurements to support the accommodative effect of the Crystalens, and these clinical benefits have been reconfirmed in this pivotal study because it shows equivalent effectiveness for intermediate and near vision of the Trulign Toric when compared to the parent platform.

These are four published studies which show superior performance for intermediate vision and near vision of the Crystalens when compared to standard non-accommodating monofocal intraocular lenses. The first study, by Marian Macsai, was discussed already by Dr. Glasser. The other studies, although they have a smaller  $n$ , also show statistically significant superiority for the Crystalens.

A published study by Dr. Pepose, appearing in the *American Journal of Ophthalmology* in 2007, compared the Crystalens with then-

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available multifocal lenses, the ReSTOR and the ReZoom. And at four to six months postoperatively, the eyes with the Crystalens achieved statistically better, best spectacle corrected distance vision as well as better uncorrected and distance corrected intermediate and best corrected near vision, and as expected, better contrast sensitivity versus multifocal intraocular lenses.

An additional four studies have described the function of the Crystalens without a specific comparison to a monofocal control. But the data from these studies also support superior intermediate and near uncorrected and distance corrected vision for the Crystalens.

A recent meta-analysis of accommodating IOLs examined the hypothesis that the accommodative effect is due to anterior axial movement. This meta-analysis showed that while studies generally report anterior movement of an accommodative optic up to .84 mm, there are heterogeneous results, and some studies actually show posterior movement. Pharmacologic accommodative studies have been criticized because the effect of pilocarpine can vary with iris color, for example, and it's not as accurate as direct stimulation of accommodation. At least one study with optic stimulation of accommodation has also shown anterior movement of accommodative intraocular lens of .33 mm.

Taking this growing body of evidence from the peer-reviewed published literature, I would say axial movement of the Crystalens certainly appears to constitute an important component of its mechanism of action.

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Personally, I have measured patients with the iTrace aberrometer and, as Dr. Glasser previously showed, documented in a paper I presented at the American Society of Cataract and Refractive Surgery Symposium in 2004 a power change in an eye with Crystalens of approximately 1.6 diopters.

When we look at the clinical performance, in terms of distance corrected near visual acuity, studies show that a monofocal standard lens, a non-accommodative monofocal, achieves distance corrected near vision on the order of 20/90; as you see here, with the CeeOn 911A, 20/87. In this study, the Crystalens control and the Trulign Toric achieve distance corrected near visual acuity of 20/40. Another study of a multifocal lens showed that with a multifocal, diffractive optic, patients achieved monocular distance corrected near of about 20/30.

Now, these studies compared are not, strictly speaking, apples to apples. The testing distances are slightly different; the methods are slightly different. But the end result is irrefutable, that the accommodative optic provides better distance corrected intermediate and near vision than a standard monofocal, and vision not that much different from that achieved with a multifocal lens.

When we look at the uncorrected intermediate visual acuity for the Trulign Toric when compared to currently available diffractive, multifocal, presbyopia-correcting lenses, we can see that the accommodative lens outperforms these multifocals at the very important intermediate distance.

And this performance is not due to residual myopia or intended "mini-monovision." As we can see, the uncorrected near is very close to the distance corrected near, and the uncorrected intermediate is very close to the distance corrected intermediate. So that takes out of the equation the effect of residual myopia.

In addition, I'd like to remind you that Study 650 is a monocular study, but accommodation is a binocular process. And clinical experience and published data show that we should expect at least a line of improvement with binocular summation when patients are able to use both eyes to focus up close.

You've seen in the data that the difference between the toric and the parent platform spherical accommodative lens vanishes at intermediate and near, and you may wonder why this is. If we think about the approximately one diopter of accommodation that the Crystalens provides, we realize that the testing distances are closer than that. Intermediate would require 1.25 diopter, and near, 2.50. So we're actually inside of the expected range of accommodation. At these distances, the effect of pseudophakic presbyopia caused blur, which tends to blur the distinction between the parent platform spherical and the Trulign Toric intraocular lenses, as you can see from these convolved E's.

In addition, residual against the rule astigmatism in the control group may benefit uncorrected near visual acuity, and the uncorrected

astigmatism is not resolved by correcting for manifest refractive spherical equivalent. In addition, as the toric optic shifts forward for accommodative effect, the correction of astigmatism of the toric optic changes, and in some eyes, that will reduce the correction and therefore lead to additional blur in the eyes with the toric lens.

So for all these reasons, the distinction between the spherical control and the toric becomes blurred at intermediate and near.

The approved labeling for the Crystalens is one diopter of accommodation. And so we expect continuous best vision from distance to within a meter. Our clinical experience shows that it actually outperforms this labeling with about 20/20 vision at intermediate. And 80% of patients in the AT45 PMA said they could use the computer without glasses. Some patients do need a low-powered pair of reading glasses for fine print at near, and I think these are reasonable expectations for our patients.

Let's look now at the toric optic and its benefits for uncorrected distance visual acuity. The lens axis misalignment from target at four to six months is less than 5 degrees, and the mean residual refractive cylinder for all the toric cohorts is below .50 diopters.

FDA has raised a concern regarding gender and age effects. As you can see in this forest plot, there is no statistically significant difference between the effect for male and female subjects. We do see a rather broad confidence interval for subjects under the age of 60, and I would like to point

out there were only seven subjects in the toric cohort. This is consistent with the fact that, demographically speaking, only 10% of Americans under the age of 60 have cataracts. So very few were in this study.

There's such a small number here that it is not appropriate on a statistical basis to draw conclusions from this small number of subjects under 60. But I would ask you, from a clinical perspective, if the correction of astigmatism is really different if you're 50 years old or 80 years old. I think we all know, as practicing ophthalmologists, that astigmatism is astigmatism regardless of age.

The uncorrected distance visual acuity is the main improvement that we see with the addition of the toric optic. And if we compare the Trulign Toric to the market leader today, the AcrySof Toric, we can see that it actually performs slightly better due, again, to its superior rotational stability.

One way of looking at spectacle independence since we couldn't address it directly in a monocular study is to ask how many subjects have an uncorrected vision within one or two lines of their best corrected vision? 84% of the all toric cohort had an uncorrected visual acuity that was within two lines of their best corrected. And 65% had an uncorrected acuity within one line. And since 20/20 was the best corrected, 71% were 20/25 or better without glasses.

When we look at intermediate, we can see that the mean is

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20/20 or close to it, and the vast majority are 20/30 or better. When we look at near, 20/40 was the mean, but again, the vast majority are 20/50 or better.

We did see a reduction in the need for glasses in this study, but it was not systematically studied, again, in a monocular trial. However, real-world examples of visual acuity at near show that these subjects will be able to read a tablet, read their smartphone or a novel without glasses.

I asked my cataract patients if they would like to reduce their need for eyeglasses after surgery because we have now available many products intended to do just this. These options include monovision, which can be great for someone who has tried it already, but when you're 70 years old with dry eye and a cataract, it may be not a good time for a contact lens trial. Multifocal IOLs can achieve a high degree of freedom from glasses, but we suffer compromised contrast sensitivity, dysphotopsia, and really these are contraindicated in patients with concomitant ocular disease.

As you've seen from the data presented today, the Trulign Toric provides superior distance and intermediate visual acuity when compared to standard monofocal IOLs, does not compromise quality of vision, and provides functional near vision to reduce spectacle dependence and provide a better quality of life for our patients. No new risks were introduced by adding the toric optic, and the current risks are already well known and understood, and those are the risks of cataract surgery in general and a

specific risk unique to this parent platform with which we have over 10 years of experience and of which the incidence has been declining. The increased benefits from correcting astigmatism are, specifically, superior uncorrected distance vision and a reduced need for secondary surgical procedures, such as LASIK, to correct residual astigmatism.

I believe this lens will provide for my patients an enhanced quality of life. Thank you very much for your consideration.

DR. HIGGINBOTHAM: Sponsor, by our calculation, you have four more minutes. Do you have any additional comments?

DR. PACKER: We'll use the time to answer any of your questions.

DR. HIGGINBOTHAM: Thank you. I would like to thank the Sponsor's representatives for their presentation.

Does anyone on the Panel have a brief clarifying question for the Sponsor? Please remember, Panel, that you may also ask the Sponsor questions this afternoon during the Panel deliberations.

Any questions now?

Dr. Coleman?

DR. COLEMAN: Yeah. I had question regarding the 10 subjects that got the AT52. I wasn't clear why that protocol deviation occurred, like, why the investigators wanted that implant or why it was inserted instead of the standard one that was being tested in the PMA.

MS. McEACHERN: Denise McEachern, Bausch & Lomb. In our original protocol that we submitted to the IDE, we were looking at the 17 and above powers, and in that particular -- at that particular point in time, that was the AT50 and the AT52 that was available, the AT50 being in the marketplace. In a subsequent supplement, we requested approval to go to lower power range below the 17, which would have taken us into the AT50 and the AT50 -- I'm sorry the AT52 and the AT52T lens. That lens was only available for the surgeons in the commercial arena as the control lens in the 52. When we asked for that approval, we were granted the approval to go to the lower power. We thought we had approval to go to the longer diameter, and subsequently FDA informed us when we submitted the package we did not.

DR. HIGGINBOTHAM: Any other questions?

Dr. Kim?

DR. KIM: If I could ask, in the study in the low astigmatism group that got randomized, were the patients, or I guess the technicians who were checking their vision postoperatively blinded to the lens that the patient received?

DR. HAYASHIDA: This is Jon Hayashida, Bausch & Lomb. They were not masked, no. That's correct.

DR. HIGGINBOTHAM: Any other questions from any of the Panel members?

Yes, Dr. Bradley?

DR. BRADLEY: I'm not sure you told us the mean refraction spherical equivalent postop. Perhaps I missed that.

DR. HAYASHIDA: Yes. We'll be pulling up that data for you.

UNIDENTIFIED SPEAKER: I didn't hear --

DR. BRADLEY: Yeah, I didn't --

DR. HIGGINBOTHAM: Could you repeat your answer, please?

DR. BRADLEY: -- hear what you said.

DR. HAYASHIDA: Oh, yes. We'll be pulling up that data.

DR. BRADLEY: Okay.

DR. HAYASHIDA: We're looking for the MSRE data, please.

DR. HIGGINBOTHAM: And please state your name.

DR. HAYASHIDA: Oh, Jon Hayashida.

DR. BROWN: One more question. Jeremiah Brown. In the manufacturing process, is the toric optic added onto the parent IOL, or is it constructed as one unit?

MS. McEACHERN: Denise McEachern, Bausch & Lomb. It's constructed as one unit. It's a molded lens. So the posterior surface has the toric correction.

DR. HIGGINBOTHAM: Thank you, Dr. Brown.

Any other questions?

(No response.)

DR. HIGGINBOTHAM: I have a question -- oh, Dr. Evans?

DR. EVANS: Yes, Scott Evans. Thank you for the informative presentations. I had a couple of questions about the theme around these interim analyses, and my understanding is that they were unplanned. And I was wondering if you could just reiterate the rationale for conducting them and some details about their conduct? Who conducted them, what was evaluated at that time in terms of were hypothesis tests conducted on endpoints and so on, what were those results, and who had privy to those results? Thank you.

DR. PEPOSE: Dr. Jay Pepose, medical monitor. There were two interim analyses that were performed, as you mentioned. Well, the first one was performed early on. At the time, there were 35 patients of the 229 subjects who were available. That was for planning purposes for another potential toric clinical trial. It was not a hypothesis-driven analysis at all.

The second analysis was performed using the Form 3 data, not the effectiveness data, and that was used basically to simulate the format and the presentation of the clinical data.

DR. HIGGINBOTHAM: Dr. Kim?

DR. KIM: I'm not sure if I ask or in the Panel deliberation, but would you say -- I don't think it's listed in the DFU, but is there a preferred orientation for the original Crystalens, the accommodating lens original platform in terms of 12 and 6, 3 and 9?

DR. PACKER: This is Mark Packer. There was not in the DFU a preferred orientation.

DR. KIM: Would you say those are commonly preferred orientations, though, in practice of where the lens should be oriented in terms of effectiveness?

DR. PACKER: This is Mark Packer. I would not say there is a common or conventional agreement on particular placement for the Crystalens axis.

DR. KIM: Okay. Because obviously, with the toric lens, it would have to be oriented -- with the astigmatism, if there was any preferred or effectiveness questions, and that would be important. And just one last one. Were there any overcorrections in terms of the astigmatism correction, someone who their axis essentially was flipped from overcorrection?

DR. PACKER: This is Mark Packer. The primary effectiveness endpoint for the study by ANSI standards is the magnitude of postoperative refractive cylinder. It's an absolute scalar quantity, not a vector quantity. So the axis or vector quantity of the postoperative astigmatism is not part of the effectiveness analysis. Small amounts of residual cylinder, on the order of, as you saw, a mean of less than .50 diopters for all the groups, were at a variety of axis locations.

DR. HIGGINBOTHAM: Dr. Feldman?

DR. FELDMAN: Yes. Initially, lens misalignment, as determined

by postoperative manifest refraction and vector analysis, was listed as a secondary endpoint, and this was dropped and was not given -- can you tell us the reason for that?

DR. HAYASHIDA: Yes. This is Jon Hayashida, Bausch & Lomb. What we found was that using vector analysis for the purpose of predicting results and the position of the IOL is somewhat flawed due to errors in the subjective refraction especially at low magnitudes of cylinder and the assessment of corneal power. Therefore, this technique wasn't deemed to be suitable for predicting the postoperative position of the toric IOL especially in light of the precision of the photographic measurements that we had. And this was also agreed upon by the agency as well.

DR. HIGGINBOTHAM: Dr. Steinemann?

DR. STEINEMANN: YAG capsulotomy is listed as a treatment strategy for asymmetric vault, but a lot of these patients will probably have capsulotomy for capsular haze and visual performance, so were there any patients that experienced problems after capsulotomy with respect to vault, rotation, or visual performance?

DR. PEPOSE: Dr. Jay Pepose, medical monitor. No. In this study -- in fact, the patients were studied and rephotographed before and after YAG capsulotomy. And there was no change in either the absolute lens axis misalignment, the signed lens axis misalignment, or rotational stability pre- and post-YAG.

DR. HIGGINBOTHAM: Thank you.

Dr. Harris and then Dr. Owsley?

DR. HARRIS: This is David Harris. I had a question about surgically induced astigmatism between the control group and the toric lens group. Since the people in the toric lens group, the surgeons, were having to modify their -- maybe modifying their position of incision differently -- I wasn't clear, first of all, in the control group, I'm assuming that the location of the incision was in the steep axis in that group? Correct? And did you find that -- you used a standard figure for surgically induced astigmatism. Did you find that with preop and postop measurements, that that mean value was essentially correct or the average surgical induced astigmatism matched what you planned ahead of time?

DR. PACKER: This is Mark Packer. The figure of .50 diopters of surgically induced astigmatism was agreed upon in the protocol in discussions with FDA. In the analysis, postoperatively, the actual mean SIA was about 0.7 diopters for both the toric and the control. There was no difference in incision placement or construction between the randomization cohorts.

DR. HIGGINBOTHAM: Dr. Owsley?

DR. OWSLEY: Should I assume that you're using change in spectacle use as your surrogate for quality of life?

DR. PACKER: This is Mark Packer. Based on published survey results, for example, from Javitz and Steinard (ph.) in the late 1990s and

validated questionnaires, I think we can safely say that reduction of spectacle dependence does enhance quality of life. However, I would just like to remind the Panel that in this trial, being a monocular study, we really cannot draw any specific conclusions about spectacle independence because the fellow eye may have been treated in a variety of ways.

DR. HIGGINBOTHAM: Yes, Dr. Owsley?

DR. OWSLEY: So in your graph on page 65 at the bottom, there is no difference between the control and the experimental groups?

DR. PACKER: In the reduction of spectacle independence graph, the high toric group was statistically significantly different from the other three groups, but the other three were similar.

DR. HAYASHIDA: This is Jon Hayashida. I was wondering if I might be able to address Dr. Bradley's question.

DR. HIGGINBOTHAM: Yes.

DR. HAYASHIDA: Okay. Thank you. Dr. Bradley, the mean MRSE for the all toric cohort was -0.28 diopters. Thank you.

DR. HIGGINBOTHAM: Any other questions?

Dr. Steinemann and then Dr. Evans?

DR. STEINEMANN: As a follow-up to your point about the high toric group and the independence from spectacle use, that high toric group, actually, it was a very small dataset, smaller than would be expected to achieve statistical significance, I believe?

DR. HIGGINBOTHAM: Dr. Evans?

DR. EVANS: So my understanding was the trial was a single-masked. I was wondering if you assessed how successful the masking was.

DR. HAYASHIDA: Jon Hayashida, Bausch & Lomb. I don't believe we assessed that.

DR. HIGGINBOTHAM: Could you repeat that for the Panel?

DR. HAYASHIDA: Okay. We did not assess the success of masking.

DR. HIGGINBOTHAM: Dr. Bressler?

DR. BRESSLER: Neil Bressler. Just to clarify, could you state again who was masked in the -- what was the single-masked? Who was it that was masked?

DR. HAYASHIDA: This is Jon Hayashida, Bausch & Lomb. The subject was masked.

DR. BRESSLER: Thank you.

DR. HIGGINBOTHAM: Was there any response to Dr. Steinemann's comment?

DR. PACKER: This is Mark Packer. The protocol specified a minimum number of subjects to be enrolled in the highest toric cohort. The randomized cohort, however, is just the low power cohort. When I was talking about reduced spectacle dependence, that analysis is just done on that one questionnaire, one item of the questionnaire, "How often do you

use spectacles?"

DR. HAYASHIDA: This is Jon Hayashida. I think one thing to consider is that this trial was really intended to evaluate a toric IOL, so we used the guidances established for that. So the randomized arm was to establish the effectiveness of the lowest toric arm, and then we enrolled a smaller number of subjects in the higher toric arm because if the effectiveness is not established in the lowest toric arm, effectiveness is not then established for the highest toric arm as well. The intent of this trial wasn't to establish formally spectacle use or spectacle independence given that it was a unilaterally implanted trial, and so that was just one question that was part of our subject questionnaire to fundamentally evaluate visual disturbances.

DR. HIGGINBOTHAM: Okay. This is Dr. Higginbotham. I have a couple of questions. I'd like to follow up on Dr. Owsley's question about quality of life. Were patients not asked about their satisfaction following the surgery?

DR. HAYASHIDA: This is Jon Hayashida, Bausch & Lomb. Yes, they were not asked about satisfaction. I don't believe they were. Again, they were asked about just one question on the use of glasses. Then the balance of them were really about how they experienced interference of their vision to perform the various activities.

DR. HIGGINBOTHAM: Okay. So they were -- it was more of a

functional line of questioning, correct?

DR. HAYASHIDA: Yes, doctor. It was primarily to assess the induction of significant visual disturbances for these subjects implanted with the toric IOL.

DR. HIGGINBOTHAM: So as a follow-up, I'd like to explore whether or not there was any potential relationship between -- recognizing you had such a small number, less than 60, but certainly there was a wide variation in terms of, you know, how those folks responded versus the other end of the spectrum -- was there any relationship between age and the responses to those subjective questions or functional questions that you just indicated?

DR. HAYASHIDA: This is Jon Hayashida. We did not evaluate formally the patients that had their visual disturbances relative to the younger than 60 age group primarily because there were few subjects that were in that cohort, but yes, we did not formally evaluate that stratified by age.

DR. HIGGINBOTHAM: Any other questions?

(No response.)

DR. HIGGINBOTHAM: Do you have a question, Barbara? No? Okay. Okay. All right. Thank you. All right. Seeing no questions or body language suggesting that there may be a question, I believe we can now declare a break. And I did investigate whether or not there was another set

of restrooms beyond the ones that are opposite Starbuck's. There is a set of restrooms next to the bar in the front of the hotel. Panel members may actually exit stage right, my right, and get to the hallway faster, but only Panel members.

(Laughter.)

DR. HIGGINBOTHAM: So we will now take a 10-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves, including in the restrooms, or with any member of the audience. We will resume our meeting at 11:00 on the dot. Thank you.

(Off the record at 10:50 a.m.)

(On the record at 11:02 a.m.)

DR. HIGGINBOTHAM: Now it's 11:02, and I would like to call this meeting back to order.

FDA will now give their presentation. I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

FDA is at the podium and ready for its presentation, and so I'd like to welcome our first presenter. FDA has 85 minutes.

Don?

MR. CALOGERO: Good morning. My name is Don Calogero, and I'm a biomedical engineer in the Division of Ophthalmic and ENT Devices

and the Engineering Reviewer for the Trulign PMA supplement.

I will be providing a brief overview of the regulation of IOLs in this presentation.

DR. HIGGINBOTHAM: Excuse me, Don --

MR. CALOGERO: Yeah?

DR. HIGGINBOTHAM: Can you come closer to the microphone.

The acoustics --

MR. CALOGERO: Okay. Is that better?

DR. HIGGINBOTHAM: That's a little better. Thank you.

MR. CALOGERO: Okay. Currently, there are more than three million cataract surgeries performed each year due to the aging of the population. Most patients are implanted with a monofocal IOL. Premium IOLs are new types of IOLs that are intended to provide benefits beyond treating aphakia. These include multifocal, toric, accommodating, and phakic IOLs. Currently, about 13% of patients are implanted with premium IOLs. All IOLs are Class III medical devices and require premarket approval.

There are 59 original PMAs that have been approved by FDA for monofocal IOLs. Most of the hundreds of different IOLs that are on the market are modifications of the original IOL approved in the PMA. FDA-recognized standards provide recommendations on the preclinical requirements and the clinical study design for IOLs.

There are currently approved PMAs for three multifocal IOLs,

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one accommodating IOL, two toric IOLs, and two phakic IOLs. Many of these approved PMAs have modifications approved through supplements to these PMAs.

There are many premium IOLs in the pipeline that incorporate one or more of these premium features, including the one to be discussed at today's meeting. Even though there is a comprehensive group of standards for monofocal IOLs, there is an incomplete group of recognized standards for premium IOLs, with many standards still under development.

FDA has been working with the American National Standards Institute and International Standards Organization since the 1980s to develop ophthalmic standards in these three categories: ophthalmic implants, contact lenses and care products, and ophthalmic instruments. An FDA-recognized standard is a consensus standard that FDA has evaluated and recognized for use in satisfying a regulatory requirement and for which FDA has published a notice in the *Federal Register*. There are 36 recognized ophthalmic standards today.

The IOL preclinical requirements are described in the recognized ISO and ANSI standards on the slide. In some cases, these preclinical requirements apply to all types, for example, biocompatibility or shelf life. We also recognize Part I, which is an IOL vocabulary standard. Ophthalmic standards are somewhat unique in that they usually provide a recommendation for the clinical investigation when it is needed.

Currently, there are recognized monofocal, multifocal, and phakic IOL standards that contain clinical annexes shown on the slide. It should be noted that the basic historical clinical safety and effectiveness data once referred to as the FDA grid is now incorporated into ISO 11979-7 as safety and performance endpoints, SPE.

There is also FDA-recognized technical report 22979 that describes how IOL modifications to monofocal and multifocal IOLs only are handled. It should be noted that this technical report defines parent IOL as having undergone a clinical study with at least 100 subjects and meeting the other non-clinical requirements in the ISO 11979 series. Work is beginning on revising this technical report to include modifications to other types of IOLs.

There is currently one toric IOL standard that has been published and is awaiting FDA recognition, ANSI Z80.30. This standard provides clinical recommendations for the study of a new toric IOL that is a modification of an approved parent IOL. This is the most common case.

The study design recommends a control study only for the lowest cylinder power aphakic toric IOL. The higher aphakic toric IOL cylinder powers and the phakic toric IOL study are uncontrolled. The study is designed to demonstrate both reduction of cylinder and rotational stability of the toric IOL.

The minimum sample size for the toric IOL study is 100 eyes. At least 62 are recommended at the lowest cylinder power to assess

effectiveness, and at least 10 are recommended at the highest cylinder power to assess visual disturbances. In cases where the requested cylinder power exceeds 2 diopters at the corneal plane, the standard recommends at least 50 eyes to assess visual disturbances.

The control group for the lowest cylinder aphakia case is a non-toric version of the toric IOL. The recommended study duration is until rotational stability is demonstrated, but at least four to six months. The outcomes are reduction of cylinder, lens axis misalignment, visual disturbances, and adverse event rates. The performance criteria in the standard are, for rotational stability, as you heard previously, 90% of subjects within 5 degrees between visits three months apart and the ISO safety and performance endpoints.

There is a corresponding ISO toric IOL standard under development which will be incorporated into the revised 11979-7 standard.

There are currently two accommodating IOL standards under development and close to completion: ANSI Z80.29, under development since 2004 -- this development began after the original Crystalens approval; and the revised ISO 11979-7, under development since 2007.

There are currently common consensus recommendations in these two standards, as follows. The study design includes two phases: Phase 1 is a control study to assess objective accommodation and safety, and Phase 2 is to assess safety and the magnitude and consistency of the

accommodative performance.

The recommended minimum accommodative IOL sample size is 300 eyes, 50 in Phase 1 and an additional 250 in Phase 2. The control sample size is 122 eyes, 50 in Phase 1 and an additional 72 in Phase 2.

The study duration for Phase 1 is four to six months, the Form 4, and for Phase 2, until accommodative stability is demonstrated, a minimum of one year and a maximum of three years.

The performance criteria for Phase 1 are a minimum average objective accommodation of at least one diopter and the ISO safety and performance endpoints. Performance criteria for Phase 2 are also a minimum average objective accommodation of at least one diopter, the ISO safety and performance endpoints, and not a statistically significant decrease in objective accommodation over six months.

The outcomes for Phase 1 and Phase 2 are the same, contrast sensitivity, visual disturbances, adverse event rates, and objective accommodation. The objective accommodative amplitude testing is a sub-study in the standard, with a minimum sample size of 100 accommodative IOL eyes and 50 control eyes. It recommends testing at six-month intervals until stability is demonstrated.

It should be noted that acceptable ANSI objective accommodation methods include optical and biometric methods, whereas acceptable ISO methods only include optical methods and are defined as

autorefractor and aberrometer.

Sue Jones will now introduce P030002 Supplement 27. Thank you.

MS. JONES: Thank you, Don.

I'm Susanna Jones, Team Leader for the subject PMA supplement, P030002, Supplement 27 for the Trulign Toric Accommodating Posterior Chamber Intraocular Lens.

I'd like to acknowledge the FDA reviewers involved in the review of this application who are shown here on this slide.

Bausch & Lomb has submitted this application for the Trulign Toric Accommodating Posterior Chamber Intraocular Lens, IOL. This PMA is brought to Panel for consideration because the Trulign IOL represents a first-of-a-kind IOL, combining toric and accommodating features. We wish to solicit the Panel's opinion on the safety and effectiveness of the Trulign IOL for the following proposed indications for use.

The Trulign Toric Accommodating Posterior Chamber Intraocular Lens is intended for primary implantation in the capsular bag of the eye for the visual correction of aphakia and postoperative refractive astigmatism secondary to removal of a cataractous lens in adult patients with or without presbyopia who desire improved uncorrected distance vision and reduction of residual refractive cylinder. The Trulign Toric Accommodating Posterior Chamber Intraocular Lens provides approximately one diopter of

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monocular accommodation which allows for near, intermediate, and distance vision without spectacles.

The subject device is a two-component system consisting of the IOL and a web-based toric calculator. The Trulign is a modified plate haptic lens with hinges across the plates near the optic. It has a biconvex silicone optic with a toric posterior surface and polyimide loops. The IOL has axis marks on the anterior surface indicating the flat meridian of the optic. The IOL has an optic diameter of 5 mm and an overall diameter of 11.5 mm. Please note that the applicant is also requesting approval for a 12 mm overall diameter version of the IOL.

Trulign Toric IOL is a modification to the currently approved Crystalens five-o IOL. The major difference between the proposed Trulign Toric and the Crystalens five-o is the incorporation of a toric posterior optic surface. The web-based toric calculator is software designed to aid surgeons in determining the appropriate toric model to implant. This toric calculator can be accessed via the Internet and recommends IOL cylindrical power and placement axis using preoperative keratometry, phaco and insertion incision location, and estimated magnitude of surgically induced astigmatism (SIA) inputs entered by the physician.

Preclinical studies included optical and mechanical testing, biocompatibility, sterilization, packaging and shelf life, manufacturing, and software validation and were found to be satisfactory.

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The regulatory history of the subject device begins with the original Crystalens Accommodating IOL. The Crystalens Accommodating IOL, Model AT45, with a 4.50 mm optic, PMA P030002, was granted approval on November 14th, 2003. The Crystalens models AT50SE and AT52SE and the Crystalens HD are modifications of the original Crystalens AT45 IOL, and the modifications are shown in blue.

As stated in our device description, the Trulign Toric Accommodating IOL is a modification to the currently approved Crystalens AT50 and 52SE IOL. The major difference is in the incorporation of a toric posterior optic surface.

The additional study for the Crystalens Toric IOL, Model AT45T, was approved under IDE G990163, Supplement 23, in November 2004. This study was suspended in Supplement 36 of the IDE in May 2007 due to two reports of unanticipated adverse events. The IOLs from both subjects in this initial study were explanted.

After the applicant performed a root cause analysis, a pilot study of 10 subjects of the Model AT45T IOL was approved in Supplement 46 of the IDE in May 2009. This study was meant to assess the corrective actions instituted by the applicant.

In April 2010, Supplement 49 for the pivotal study for the subject device, the Model AT50T IOL, was approved.

In May 2012, P030002, Supplement 27, for the subject device,

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the Trulign Toric Accommodating Posterior Chamber IOL, was filed.

Subsequent amendments to the application have been received through January 13. While the information submitted in the final report has not been fully reviewed, the information received up to November 2012 has been incorporated into FDA's Executive Summary and this presentation.

Now Dr. Maryam Mokhtarzadeh will present the clinical data for the PMA. Thank you.

DR. MOKHTARZADEH: Good morning, distinguished Panel members, Bausch & Lomb representatives, FDA staff, and the public. I will be presenting to you this morning the key results of the pivotal study submitted by the applicant in their premarket approval application for the Trulign Toric Accommodating Posterior Chamber Intraocular Lens and FDA's questions for Panel consideration.

Please be reminded of the proposed indications for use, which states: The Trulign Toric Accommodating Posterior Chamber Intraocular Lens is intended for primary implantation in the capsular bag of the eye for visual correction of aphakia and postoperative refractive astigmatism secondary to removal of a cataractous lens in adult patients with or without presbyopia who desire improved uncorrected distance vision and reduction of residual refractive cylinder. The Trulign Toric Accommodating Posterior Chamber Intraocular Lens provides approximately one diopter of monocular accommodation which allows for near, intermediate, and distance vision

without spectacles.

The PMA cohort data were obtained under protocol 650. The test device was the Model AT50T Trulign Toric Accommodating IOL, which has an overall diameter of 11.5 mm. The toric calculator was used to determine which of three cylinder powers would be implanted in eligible subjects. The control used in this study was the spherical Crystalens Accommodating IOL, Model AT50SE.

The applicant conducted a clinical investigation that was a prospective, multicenter, single-masked, partially randomized and partially controlled study. Bilateral implantation of the test device was not permitted in the study.

Duration of subject follow-up was based on establishment of rotational stability up to a maximum of one year.

The study was separated into two groups: one randomized with a control IOL, the other non-randomized. The randomized group included only subjects who were eligible to receive the lowest toric cylinder power, that is, the 1.25 diopter toric IOL.

The subjects in this group were randomized to receive the 1.25 diopter toric IOL or the spherical control IOL and were masked to the implanted IOL type. The non-randomized group consisted of subjects eligible to receive the 2 diopter and 2.75 diopter toric models. This design is consistent with the ANSI toric IOL standard.

The primary effectiveness endpoint was percent reduction in absolute cylinder. Additional primary endpoints included percent of eyes with reduction of cylinder within half a diopter and within one diopter of intended and lens axis misalignment as determined by a photographic method. The primary endpoints were to be evaluated when rotational stability was achieved. This occurred at the Form 4 visit, which occurs four to six months postoperatively.

Secondary effectiveness endpoints include uncorrected acuities and distance corrected acuities. These were also evaluated at Form 4.

A primary safety endpoint was not specified due to the expectation that the safety profile of the toric IOL would be similar to that of the Crystalens AT45 IOL based on IOL design. The safety endpoints were preservation of near and distance best corrected visual acuity and incidence of complications and adverse events.

A complete listing of the surgical procedure appears in Appendix B of the FDA Executive Summary. This slide lists key aspects of the surgical procedure in the protocol, including those relevant to the expected surgically induced astigmatism. Please note that incisions were to be performed at the steep axis for all subjects, experimental and control device recipients. Please also note the absence of sutures and limbal relaxing incisions in this study.

The Trulign is a toric accommodating IOL. While this study did

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not include objective or subjective measures of accommodation, the study did assess lens axis misalignment, which is an important assessment for a toric IOL. Lens axis position was assessed through image capture with registration through ocular landmarks.

Please note the accommodative ability of the lens is believed to be comparable to that of the Crystalens AT45. However, in review of an IDE annual report, the applicant was advised that in the future PMA application for the approval of the toric modification, they would be asked to address issues related to accommodative effectiveness that had been raised in the literature.

229 subjects were enrolled at nine sites. One site was outside the U.S. and enrolled 9 subjects. There were 158 subjects in the randomized group, of which 82 were enrolled in the lowest toric cylinder power arm and 76 were enrolled in the control arm to receive the spherical IOL. The remaining 71 enrolled subjects were not randomized. Forty-seven of these subjects were enrolled in the toric 2 diopter arm, and 24 were enrolled in the 2.75 diopter arm. Please note that since this study was a monocular study, the number of subjects enrolled is equal to the number of eyes enrolled.

Of the original 229 subjects, 211 subjects were available for analysis at Form 4. Two subjects were discontinued prior to implantation, one subject discontinued after implantation, and 15 subjects were still active at the time of the PMA application.

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401 protocol deviations were identified during review of the application up to Amendment 4. These included 28 major protocol deviations and 373 minor deviations. In addition to the information presented in the Executive Summary, this includes four minor protocol deviations that the applicant reclassified to major protocol deviations in Amendment 4. While the information submitted in the final report has not been fully reviewed nor incorporated into FDA's presentation, we would like to point out that there were additional deviations, both major and minor, identified in the final study report.

During the study, the large number of protocol deviations prompted the applicant to transfer oversight and take corrective actions during the study.

Major protocol deviations included failure to meet enrollment criteria, noncompliance with the surgical protocol, and implantation of unapproved IOL models. Please note that the four major protocol deviations we list here, in addition to those in the FDA Executive Summary, consist of incisions which were not placed at the steep axis, as specified in the study protocol.

Major protocol deviations resulted in exclusion from effectiveness analyses. The 377 minor deviations include protocol assessments which were not performed or performed incorrectly, documentation practices in violation of the protocol, out-of-window visits,

consent process deviations, and missed visits.

The Panel will be asked to discuss the following question:

Given the over 400 protocol deviations ranging in severity from implantation of an unapproved device model to poor documentation practices, do you believe that the conduct of this study used to support the Trulign Toric Accommodating IOL are able to demonstrate that the benefit from the use of the device outweighs the risk?

I will now discuss key safety results. Best corrected distance visual acuity in all eyes implanted with the toric IOL was greater than or equal to 20/40 in 97.9% of eyes at Form 4. Best corrected near visual acuity in all eyes implanted with the toric IOL was greater than or equal to 20/40 in 100% of eyes at Form 4.

Adverse events in the study were categorized as cumulative or persistent FDA grid adverse events, surgical adverse events, and ocular or non-ocular adverse events. Serious adverse events were separately identified and described as ocular or non-ocular. The safety results have been presented by the applicant. I will point out a few key findings here.

Cumulative adverse events based on ISO safety and performance endpoints include two cases of macular edema and two cases of secondary surgical interventions. One case of each occurred in the control arm, and the other occurred in an eye implanted with a toric IOL. Secondary surgical interventions were necessary for two study eyes. One case involved

IOL vaulting at Form 4, occurring for this subject approximately four months postoperatively, and the other was a case of IOL malposition identified at postoperative day one.

Ocular serious adverse events can occur in either eye of a study subject. The events reported in this trial include two total cases of IOL vaulting and one case of IOL malposition. One of the vault cases occurred in a non-study fellow eye implanted with a Crystalens IOL. The other cases were mentioned on the last slide as events which led to secondary surgical interventions in study eyes.

In this application, the applicant has stated: "The Crystalens is designed to vault forward with ciliary muscle contraction when focusing at near and return to its original position with ciliary muscle relaxation when focusing at distance. The anterior vaults listed as an adverse event does not refer to this expected movement of the Crystalens, but rather to the condition that occurs when the lens optic becomes lodged in an anterior position independent of ciliary muscle relaxation or contraction, that is, whether the patient is focused at distance or at near."

The applicant has also defined Z-syndrome in this application: "An asymmetric combination of capsular contraction forces and vitreous pressure can result in the anterior vault of one hinge and the posterior vault of the other hinge. This creates an asymmetric tilt of the Crystalens, also known as Z-syndrome."

Please note that the definition of Z-syndrome in the literature is slightly different. Jardim et al. have reported that "Asymmetric vault is a postoperative complication unique to the accommodating Crystalens IOL. Because of irregular capsule contraction, one haptic is pulled anteriorly while the other remains in the normal posterior position. The IOL configuration in the capsular bag resembles the letter Z, with the tilted optic in the middle."

In the Trulign study, there were two cases of IOL vaulting reported in 229 subjects. Both cases were detected at the Form 4 visit, which occurred for both subjects approximately four months postoperatively for the affected eye. One case was attributed by the applicant to noncompliance with medications, resulting in atypical fibrosis of the capsular bag and capsular contraction.

It is important to note that based on case report forms, no cell, no flare, and no corneal stromal edema were noted at the Form 2, Form 3, or Form 4 visits. At Form 1, which occurs one to two days postoperatively, there was mild central corneal stromal edema and one plus cell and no flare. It is unclear from this clinical picture when noncompliance may have occurred, but the investigator determined that noncompliance occurred after identifying this adverse event four to six months postoperatively. After an IOL repositioning procedure, the toric IOL axis was misaligned by 56.84 degrees. This subject was eventually lost to follow-up.

The second case was attributed to zonular dehiscence.

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However, zonular dehiscence was discovered after an IOL repositioning procedure, subsequent explantation of the IOL, and attempted implantation of another Crystalens which immediately vaulted. Due to the behavior of the two IOLs, the investigator suspected zonular dehiscence, so the investigator chose to implant a monofocal IOL with fixation in the sulcus. It is unclear based on the various surgical manipulations performed prior to the investigator's suspicion of zonular dehiscence at what point the suspected dehiscence may have occurred and, therefore, whether it contributed to the initial vaulting.

In the original Crystalens study of 324 subjects and 497 implanted eyes, there was one case of IOL explantation due to anterior vault. The labeling for the Crystalens AT45 IOL identifies anterior vaults as an adverse event and includes some precautions. Following initial approval of the Crystalens AT45 IOL, a supplement was submitted with labeling revisions attempting to mitigate this adverse event. These revisions included a 5.50 to 6 mm capsulorhexis size, meticulous cortical cleanup and IOL rotation to dislodge cortex, and a postoperative medication regimen with anti-inflammatories tapering over a minimum of four weeks.

To better understand the scope of vaulting with the Crystalens models, FDA has analyzed additional information available. This information includes MDR analysis and review of the published literature.

The MDR analysis was conducted by the Division of Postmarket

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Surveillance within the Office of Surveillance and Biometrics. The FDA Medical Device Reporting system is a nationwide passive surveillance system. Medical device reports, or MDRs, are received and entered into the Manufacture and User Facility Device Experience, or MAUDE, database, which is the FDA's database for collecting medical device adverse event reports.

The MAUDE database includes both mandatory and voluntary reports. Manufacturers and importers are required to submit reports to FDA of device-related deaths or serious injuries as well as events involving a device malfunction that may cause or contribute to a death or serious injury. User facilities, most notably, hospitals and nursing homes, are also mandated to report device-related deaths to FDA and device-related injuries to the device manufacturer.

The FDA also has a voluntary reporting program called MedWatch. Anybody, including healthcare practitioners, consumers, patients and their family members can report device-related adverse events through FDA's MedWatch program by phone, fax, or online. Information on reporting can be found at FDA's website.

The MDR system, while providing signals of actual and potential device-related problems, has some limitations. These include the following.

First, underreporting of adverse events to the FDA is a well-known and recognized phenomenon. Thus, events reported through MDR

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represent a subset of the total occurrence of events.

Second, there are data quality issues with MDR reports. Reports received are often incomplete, and FDA does not validate the information received. For instance, a large proportion of reports do not contain information on age or gender.

Third, it is impossible to determine incidence rates from MDR data alone. The FDA does not have reliable information regarding the number of devices on the market, nor do we have all the adverse event reports, due to underreporting, so it is impossible to calculate the incidence rate.

Fourth, reports received may not be representative and reflect a variety of reporting biases. For example, reporting may vary by manufacturer and by the presence or absence of publicity. Also, we receive a variety of narratives for the same device depending on the report source. For instance, a voluntary report's narrative can be completely different from a manufacturer's narrative for the same product and the same adverse event.

Fifth, it is generally not possible to infer cause and effect relationship from individual reports. Furthermore, most reports do not contain results of manufacturer failure analyses. Often devices are not returned to the manufacturer for evaluation because they are discarded or remain implanted.

Now I will describe the search methodology used to obtain the

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dataset of Crystalens Accommodating Intraocular Lens reports in this presentation. The database was searched using two search criteria: first criteria was brand name Crystalens; second one was date report entered up to January 25th, 2013.

The search found a total of 1,268 reports associated with the Crystalens IOL. These reports included 1,248 reported by the manufacturer and 20 reported by voluntary reporters. 1,106 were injury reports, and 162 were malfunction reports.

The number of reports received by year over the last 10 years is shown in this table. The highest number of reports was in 2007 and 2008.

1,268 reports were reviewed and grouped. Each report was only counted once during categorization. A total of 271 MDRs were believed to be most relevant to IOL vaulting. These are presented on this slide.

This table shows the number of reports in other categories. The lens damage category contains mostly reports of IOL haptic breakage. The vision disturbances category include reports of glare, halos, blurry vision, double vision, night vision, decreased best corrected visual acuity, and poor vision outcome. A few reports in this group described clinical case histories that may be relevant to vaulting, but this was atypical for the majority of reports in this category. Finally, events related to capsular bag tears and insertion issues were separate categories. A total of 911 MDRs fell into these categories that were mostly unrelated to vaulting.

The following slides present the results from a systematic literature review on Crystalens and IOL vaulting conducted by the Division of Epidemiology within the Office of Surveillance and Biometrics. The systematic literature review was conducted to address vaulting as a unique safety concern of Crystalens.

Embase and PubMed were searched by device name and all model names and numbers. The search was limited to human studies in English from the year 2000 to 2012.

The initial search yielded 131 citations, with 130 unique citations after one duplicate was excluded. In the first round of exclusions, by a review of titles and abstracts, 88 articles were excluded. Because the search included model names, many articles were not related to the target device. Also, article types included letters to the editor, commentaries, and non-systematic reviews. These article types were excluded as non-studies.

Full texts of the remaining 42 studies or case reports on Crystalens were examined by reviewers for inclusion, of which 38 were excluded because they did not report IOL vaulting. Please note that this is a change from the numbers originally presented in the FDA Executive Summary as six of the articles initially included did not report the adverse event of interest and includes an additional case report.

In the end, our systematic literature review included four articles on IOL vaulting. Four articles reported on vaulting or Z-syndrome.

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There were three case reports, with a total of four subjects. There was also a retrospective chart review of 28 subjects with 35 eyes, which found one case of vaulting. These articles were published between 2005 and 2008.

In summary, we are aware of the following information on IOL vaulting: First, there were two case reports in the current Trulign pivotal study out of 229 subjects and eyes. Next, one case occurred in the original approval study for the Crystalens IOL out of 324 subjects and 497 eyes. MDR data includes approximately 271 reports of events related to IOL vaulting. Please note that the case occurring in a non-study eye during the Trulign study may have been reported as one of these MDRs.

When evaluating the literature, FDA determined that there was limited discussion in the literature related to the issue of IOL vaulting. There were only five total subjects, four subjects from three case reports and one case from a retrospective chart review, experiencing severe lens tilt or vault change or Z-syndrome caused by capsular fibrosis.

Although each source reports only one to two cases, please note that consequences of IOL vaulting can stretch beyond a single secondary surgical intervention. For example, in case reports from the current pivotal study as well as in individual MDRs, multiple surgical manipulations and/or separate procedures may be necessary to identify and/or resolve an event. These procedures may include YAG capsulotomy, IOL repositioning, IOL explantation, reimplantation of an IOL, and/or refractive surgical procedures.

The Panel will be asked the following question: We have the following information with regard to IOL vaulting: Two reports in the Trulign study, one report in the original approval study for the Crystalens, approximately 270 MDRs potentially related to vaulting and Crystalens IOLs, and five cases in the literature. In light of this information, do you believe the data support reasonable assurance of safety of the Trulign Toric Accommodating IOL?

I will now discuss key effectiveness results. Percent reduction of cylinder is the achieved reduction divided by the intended reduction. Please note that the numerator is the difference in cylinder between two different types of assessments, the postoperative manifest refraction minus the preoperative keratometric cylinder. Also, the denominator is the difference between intended postoperative manifest refractive cylinder and the preoperative keratometric cylinder. Note that the intended reduction of cylinder includes .50 diopters of surgically induced astigmatism, and that based on inclusion criteria, there were no intended overcorrections.

The primary effectiveness endpoints include the following results. In the randomized portion of the trial, subjects receiving the 1.25 diopter toric IOL showed a percent reduction in cylinder of 81.2%, and the control subjects demonstrated a percent reduction of 45.4%. Thus, the treatment effect is approximately 35.8%. This is statistically significant at  $p$  less than 0.0001. In all subjects implanted with toric IOLs, the percent

reduction was 85.6%. The statistician will address subset analyses in a later presentation.

Analysis of the percentage of eyes with reduction of cylinder within .50 diopters and within 1 diopter of intended demonstrated the following: In the randomized portion of the study, 79.7% of the subjects implanted with the toric 1.25 diopter were within .50 diopters of intended cylinder, and 95.7% were within 1 diopter. 45.3% of the control arm were within .50 diopters, and 70.3% were within 1 diopter. In all subjects implanted with a toric IOL, 79.1% of the subjects were within .50 diopters, and 95.3% were within 1 diopter.

Lens axis misalignment, as determined by a photographic method was measured relative to surgical markings. Mean lens axis misalignment for the subjects who received the 1.25 diopter toric IOL was 3.3 degrees, and it was 3.0 degrees for all subjects receiving a toric IOL.

Both mean and median absolute rotation between Form 3 and Form 4 in all eyes implanted with a toric IOL were approximately 1 degree. Approximately 99% of the eyes in this analysis showed rotation of less than or equal to 5 degrees.

Mean uncorrected acuities are reported here in Logmar. Please note that uncorrected acuities can be affected by the remaining refractive error, in other words, myopia. The results shown here indicate an observed difference in the randomized group between the control and toric

1.25 diopter arms for distance uncorrected acuities, with a p-value of 0.004. The p-values for the results of uncorrected intermediate and near acuity are 0.465 and 0.947 respectively. The applicant was asked to provide these results after adjusting for residual spherical refractive error.

For randomized eyes, the mean uncorrected distance acuities showed a benefit of 2/3 of one line for the toric arm compared to the control arm. However, at intermediate and near, the toric arm and near, the toric arm showed virtually no benefit compared to the control arm, only one to two letters.

70.7% of subjects implanted with a toric IOL in the Trulign study achieved uncorrected near visual acuity of greater than or equal to 20/40. However, 89.1% of eyes from the original approval study of the Crystalens IOL achieved uncorrected near visual acuity of greater than or equal to 20/40. Please note that the Trulign study included subjects with greater astigmatism than the original Crystalens study. Thus, some subjects in the Trulign study had residual astigmatism of greater than one diopter. This may be one reason for the poorer uncorrected acuity.

The Trulign study was a monocular study, and spectacle independence was not assessed as a formal endpoint. However, the applicant reported on a single question within a visual disturbances questionnaire that asked about the frequency of glasses use. Due to the fact that this was a monocular study, the relevance of this data is questionable.

In response to the question, 32.3% of control subjects and all toric subjects reported that they wore glasses none of the time as opposed to some, half, most, or all of the time. In contrast, during the original Crystalens study, multiple questions were asked regarding spectacle independence. Although no control subjects were questioned, 25.8% of subjects said they did not wear spectacles, and an additional 47.7% of subjects reported that they wore spectacles almost none of the time, as opposed to some, most, or all of the time.

The Panel will be asked the following question: Spectacle independence was not assessed as a formal endpoint in the Trulign monocular study. At Form 4, 70.7% of toric IOL-implanted eyes achieved uncorrected near visual acuity greater than or equal to 20/40, and 97.7% of toric IOL-implanted eyes achieved uncorrected intermediate visual acuity greater than or equal to 20/40. The proposed indications for use states that the Trulign toric provides approximately one diopter of monocular accommodation, which allows for near, intermediate, and distance vision without spectacles. Do the available data support the proposed indications for use?

Distance corrected near visual acuity were reported in both the current pivotal study and the original approval study for the Crystalens AT45 IOL. The percentage of subjects achieving a distance corrected near visual acuity greater than or equal to 20/40 was 62.9% of all subjects implanted

with a Trulign Toric IOL and 64.6% of subjects implanted with a spherical control IOL. This is compared to 90.1% of subjects implanted with the Crystalens in the original approval study. Please also note that the near acuity was a surrogate measure for accommodation in the original trial. By this measure, the IOL is performing differently in the Trulign trial compared to the original approval trial.

While the exact mechanism is unknown, the labeling for the Crystalens AT45 IOL states: "The Crystalens was designed to move in a backward and forward motion along the axis of the eye in response to pressure changes in the vitreous cavity and anterior chamber that results from relaxation and contraction of the ciliary muscle." In the approved labeling, surgeons are advised: "The optic should be vaulted backward to a position corresponding to the normal location of the posterior capsule." This is intended to improve the refractive predictability of the IOL and to maximize potential for accommodation by optimizing contact with the vitreous and allowing more forward movement of the optic."

However, speculation has been made in literature that part of the mechanism of action of the Crystalens is not due to a true overall focal shift but to increased aberrations or astigmatism from tilt related to ciliary muscle contraction. Of note, this alternate mechanism of action does not represent true accommodation, but rather, a variable depth of focus.

There were no assessments of accommodative amplitude in

the Trulign study. During the IDE, a future PMA concern was communicated regarding the potential need for accommodative assessments. The accommodative ability of the Trulign is likely to be comparable to that of the Crystalens AT45 IOL based on the similarity of the IOL design.

The accommodative evidence available from the original approval study for the Crystalens AT45 IOL included mainly improved levels of intermediate and near acuity compared to a standard monofocal IOL. Please note that this type of data does not necessarily indicate functional accommodation, and acuity can be influenced by many non-specific factors, such as blur interpretation, corneal multifocality, depth of focus related to IOL aberrations, and pupil size. Specific accommodation testing was limited to 5 subjects with 10 implanted eyes at a single site who underwent additional testing to document the mechanism of action of the IOL.

Information regarding the Crystalens HD study was not provided in this PMA application, nor was it referenced in the applicant's executive summary. Please note that the Crystalens HD has a modified lens optic with an approximately 3 micron central thickening, accounting for a 1 diopter add that extends the depth of field.

Change in anterior chamber was tested using immersion biometry. A difference of 0.62 mm in IOL position was demonstrated following exposure to 1% cyclopentolate compared to 6% pilocarpine. Please note that there was no control in this study. Please also note that the

difference was reduced to 0.23 mm when comparing the unmedicated baseline IOL position at distance compared to the IOL position after exposure to 6% pilocarpine. Finally, the difference decreased to 0.19 mm when fellow eyes were included.

In this analysis, it is an assumption that in the baseline condition of the contralateral eye was in a relaxed accommodative state for distance viewing during the A-scan. We note that only a few subjects in the study were implanted bilaterally. It is uncertain whether the eyes were actually in a relaxed accommodative state in this unmedicated testing condition.

Regarding the data from the push down test, please note that the HD model uses a unique optical design that confounds the issue of subjective accommodation assessment. Therefore, this data is also of limited evidential utility when considering the accommodative ability of the Trulign.

Please note the difference between the study design of the Crystalens HD Study and the design recommended in the current draft of the ANSI accommodation IOL standard for objective accommodation assessment. While in 2008 FDA found the study sufficient to grant approval of the Crystalens HD, this comparison illustrates an evolution of thinking with regard to important elements of an accommodation study. Note first there was no control and no masking in the Crystalens HD study. In addition, pharmacologic agents were used.

Please note that within the current Trulign application, the applicant states: "It is important to note that the utilization of pharmacologically pilocarpine-induced ciliary muscle contraction to simulate accommodation has been called into question. In fact, Kriechbaum et al. refuted this methodology and stated that pilocarpine may not simulate the actual in vivo performance of accommodating intraocular lenses."

Next, in the Crystalens HD study, measurements under two different pharmacologic conditions were taken at a minimum of three weeks apart rather than collecting data at a single study visit. Measurements under identical conditions or pharmacologic exposures were not repeated at different time points. Specific details of methodology were not included in the protocol, for example, details of instructions to technicians and patients.

The Crystalens HD study included 31 primary implanted eyes and four fellow eyes to investigate a modification to an existing IOL compared to the current recommendation of a minimum of 100 accommodating IOL eyes and 50 control eyes for an investigation of a new accommodating IOL. Finally, current recommendations include a validated conversion between biometric and dioptric values.

It has been almost a decade since the original approval of the Crystalens AT45 IOL. Since approval, there has been controversy in the published literature regarding the true accommodative ability of the Crystalens IOL. Therefore, FDA conducted a literature review to evaluate the

Crystalens accommodation data available in the literature. The same methods were used as described for the vaulting literature review. However, the PubMed search was updated separately on February 7th, 2013, yielding an additional article in this review.

The initial search yielded 132 citations with 131 unique citations after one duplicate was excluded. In the first round of exclusions, by review of titles and abstracts, 88 articles were excluded. Because the search included model names, many articles were not related to the target device. Also, article types included letters to the editor, commentaries, and non-systematic reviews. These article types were excluded as non-studies.

Full texts of the remaining 43 articles were examined by reviewers for inclusion. Of these 43 articles, only 10 articles discussed measurement of the amplitude of accommodation with a Crystalens model. Please note that other published articles assess near acuities but did not attempt to measure amplitude of accommodations. These were not covered by this review. Please also note that three articles discussed exclusively subjective measurements of accommodative amplitude. All three of these studies were done by assessing defocus curves using the Crystalens HD model. These are not discussed here because, as previously stated, the HD model uses a unique optical design that confounds the issue of subjective accommodation.

The seven remaining articles all used methods of objectively

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assessing accommodation, and three of these also used subjective measures. However, we note that subjective methods are subject to the same limitations as acuity measurements.

The objective measurements covered in the remaining seven studies included change in anterior chamber depth, optical dioptric changes using a dynamic aberrometer, refractometer, or autorefractor, and dynamic retinoscopy. These studies were the focus of our review.

Three of the seven studies included a control which was a monofocal IOL. Studies without a control group, particularly those measuring anterior chamber depth with ultrasound, can be subject to undetermined levels of poor technique or experimental methodology. Please also note that some studies used 2% pilocarpine, and studies that have used pilo have been criticized in the literature as providing unphysiologic levels of stimulation of the ciliary muscle and are likely providing only an upper limit to the amount of IOL movement or accommodation that can be generated. Please also note that several studies include less than five subjects. These studies can only provide limited information.

Four studies measured change in anterior chamber depth, or ACD, in response to accommodative stimulus. Please note that these studies only indirectly assess accommodation, and there is not a 1:1 relationship between IOL forward movement and dioptric magnitude of accommodation. The relationship depends upon axial length, corneal curvature, IOL power,

and other factors. Theoretical optical calculations indicate that dioptric change per millimeter can vary between about .8 diopters per millimeter to 2.3 diopters per millimeter. If a typical value is taken as 1.5 diopters per millimeter, then .2 millimeter movement corresponds to .3 diopters.

Mean changes in ACD in these studies varied from negative accommodative movement or deepening of the anterior chamber depth to a positive accommodative movement, specifically up to 0.3 mm. Only one study had a control. This was also the only study included in our literature review in which subjects were randomized into treatment arms.

Please note that the second Marchini study listed in the table on this slide is one of the three controlled studies in our literature review and the only study measuring the change in anterior chamber depth with a control. This was a prospective trial using a visual accommodative stimulus as opposed to pharmacologic stimulation. The data in our table is from the one-year postoperative assessment. Please note that the study also assessed patients one month postoperatively.

Of the three controlled studies, it is the only one that had measurements at multiple time points. The study demonstrated a decline between one month postop and 12 months postop in accommodative amplitude, specifically a difference between 0.24 mm at one month postop compared to 0.17 mm at one year postop. Please also note the finding in this study that by subjective assessment, the amplitude of accommodation for

the control monofocal lens was greater than for the Crystalens.

Three studies used aberrometry or refractometry to measure mean amplitudes. These studies demonstrated low, up to +0.45 diopters to negative levels of accommodation. The 2013 study by Zamora-Alejo et al. had the highest number of eyes compared to the other aberrometry/refractometry studies. Using a binocular open-field autorefractor, this study found mean accommodation to be slightly negative in both arms.

The study by Zamora-Alejo et al. had the unique advantages of utilizing a fully objective optical method that directly measures the dioptric refractive power of the eye using a matched control group of monofocal lens-implanted individuals and having sufficient numbers of subjects for meaningful results. This study concluded that there was no consistent increase in myopia with near effort for the Crystalens HD.

A single study used dynamic retinoscopy. Note that this technique is subjective on the part of the retinoscopist, depends upon his or her skill in the technique and has unknown repeatability and reproducibility. A mean amplitude of 2.42 diopters was found in subjects implanted with the Crystalens AT45.

This study was the largest study included in our review, with 112 eyes, 56 patients per arm, and used the AT45 Crystalens model and a monofocal control. Subjects were not randomized between treatments, but testing order was randomized, and the tester was masked. Using subjective

defocus testing, the study found a difference in the mean monocular amplitude of accommodation between the two arms of approximately one diopter. This study had an unusual result in that the objectively measured amplitude was greater than the subjectively measured amplitude.

Please note that the two controlled studies using subjective measures of accommodation found differences between test and control eyes of -.2 diopters in the first study, meaning the control performed better, and +1 diopter in the second, meaning the Crystalens performed better.

No objective or subjective accommodative assessments were performed in the Trulign study. Therefore, available information regarding the accommodative amplitude includes the distance corrected near visual acuity data from the current study, which demonstrates that the percentage of subjects achieving a distance corrected near visual acuity greater than or equal to 20/40 was 62.9% of all subjects implanted with the Trulign Toric IOL and 64.6% of subjects implanted with the spherical control. This is compared to 90.1% of subjects implanted with the Crystalens in the original approval study. It also includes the limited data from 5 subjects with 10 implanted eyes in the original Crystalens IOL study in addition to the anterior chamber depth and push down test data from the Crystalens HD study.

Finally, data from the literature shows mixed results. Accommodative amplitude is variable, depending on study methodology. Results range from negative, or backward, to positive accommodative

movement. Please note that an asterisk appears by the sources in this slide, which include the use of pilocarpine for some of the testing.

The Panel will be asked to discuss the following question: With regard to accommodative amplitude, there were no objective or subjective measurements in the Trulign study. Five subjects, 10 implanted eyes, were evaluated in the original Crystalens study. The Crystalens study includes biometry data from 31 primary eyes and push down test results from 33 eyes. Literature shows mixed results by objective assessments, ranging from negative to positive accommodative movement. Given the currently available information, do you believe the data support the applicant's proposed IFU of approximately one diopter of monocular accommodation?

Now Dr. Laura Lu will present the statistical considerations.

DR. LU: Good morning. I'm Laura Lu, the statistical reviewer for this PMA. I will present the statistical issues in Study 650.

First, I will briefly recap the statistical analysis plan. Then I will introduce the main results of the primary endpoint. The focus of this presentation will be on the consistency of treatment effect across subgroups.

These are some key points in the statistical analysis plan.

Patients were randomized with a ratio of 1:1 to toric lens 1.25 diopters and sphere lens groups. The sphere lens group served as the control in the study. Additional patient data were collected for the toric lens 2 diopters and 2.75 diopters groups. However, these data are not to be compared to the control

due to the lack of randomization.

Although multiple primary endpoints were proposed in the protocol, the endpoint, percent of the intended reduction in absolute cylinder, was the only one planned to be formally compared between the toric lens 1.25 diopters and control groups. Subgroup analyses were not planned in the protocol. Per FDA's request, analysis by age and gender were performed after the PMA was submitted.

This slide presents the results on percent of the intended reduction in absolute cylinder at Form 4. The observed mean percent of intended reduction is 46.3% in the control arm, 81.1% in the toric lens 1.25 diopters arm, 87.9% in the toric lens 2 diopters group, and 97.2% in the toric lens 2.75 diopters group. The toric lens 1.25 diopters group showed an observed 34.7% higher intended reduction than the control group. This advantage is statistically significant with a p-value less than 0.001. The results on this slide are based on the effectiveness analysis dataset, excluding patients with major protocol violations. FDA also conducted a sensitivity analysis, including patients with major protocol violations. The result of the sensitivity analysis is consistent with that on this slide.

Subgroup analyses were not planned in the protocol but were performed after the PMA was submitted per FDA's request. I will focus on the consistency of results across gender and age subgroups due to the level of clinical concern and statistical significance.

This slide shows the result of percent of the intended reduction in absolute cylinder by gender. The pink columns are for the toric lens 1.25 diopters group, and the blue columns are for the control group. Among male patients, the observed mean percent of intended reduction is 83.3% in the toric lens 1.25 diopters group and 36.6% in the control group. Among female patients, the observed mean percent of intended reduction is 79.6% in the toric lens 1.25 diopters group and 54.4% in the control group.

Therefore, the observed treatment effect is 46.7% in male and 25.2% in female. When testing treatment by gender interaction, namely, the difference in treatment effect between age group -- between gender, the p-value comes up as 0.1043. Although this value is larger than 0.05, it is small enough to be concerned since clinical trials are, in general, underpowered in detecting treatment by subgroup interactions.

This slide shows the results of percent of the intended reduction in absolute cylinder across age groups. As done by the applicant, patients were categorized into four age groups: less than 60, 60 to 69, 70 to 79, 80 and older. The pink columns are for the toric lens 1.25 diopters group, and the blue columns are for the control group. We observed that in the patients less than 60 years old, the toric lens 1.25 diopters group has a lower mean percent of intended reduction than the control group, while in the other age groups, the toric lens 1.25 diopters group has a higher observed mean percent of intended reduction than the control arm.

On this slide, instead of separating patients into age groups, we fit regression lines for the percent of intended reduction in absolute cylinder directly along age. The red regression line is for the control group, and the black regression line is for the toric lens 1.25 diopters group. We observed different trends along age in the two treatment groups. The observed treatment effect, which is reflected as the difference between the black line and the red line, decreases as age decreases. When testing for treatment by age interaction, the p-value comes up as 0.0002.

In summary, regarding the endpoint, percent of intended reduction in absolute cylinder, we observe a difference in treatment effect between male and female. The observed treatment effect is 46.7% in male and 25.2% in female. When testing for treatment by gender interaction, the p-value comes up as 0.1043.

The observed treatment effect is also different along age. The observed treatment effect of toric lens 1.25 diopters versus control decreases as age decreases. When testing for treatment by age interaction, the p-value comes up as 0.0002.

The Panel will be asked to discuss the following question:

Below age 60, subjects implanted with the control IOL had greater percent reduction in cylinder than those implanted with the toric IOL 1.25 diopters. In light of this, please discuss:

a. If you believe limitations by age should be added to the

indications for use and

b. What specific labeling recommendations you believe are appropriate.

Now Dr. Megan Gatski will present the post-approval study considerations.

Thank you.

DR. GATSKI: Good morning, distinguished members of the Panel and members of the audience. My name is Megan Gatski, and I'm an epidemiologist in the Division of Epidemiology Office of Surveillance and Biometrics at CDRH. I will now present the post-approval study considerations for the Trulign Toric Accommodating Posterior Chamber Intraocular Lens.

Before we talk about post-approval studies, we need to clarify a few things. The inclusion of post-approval study questions should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and benefit before the device can be found approvable and any post-approval study could be considered.

There are two general principles for post-approval studies. The main objective of conducting post-approval studies is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness. Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

The specific reason for conducting post-approval studies is to gather postmarket information, including longer term performance of the device, data on how the device performs in the real world in a broader patient population treated by community-based physicians and specialists as opposed to highly selected patients treated by investigators in the clinical trials, evaluation of the effectiveness of training programs for use of devices, evaluation of device performance in subgroups of patients since clinical trials tend to have limited numbers of patients or no patients at all in certain vulnerable subgroups of the general patient population, and to monitor adverse events, especially rare adverse events, that were not observed in the clinical trials. In addition, post-approval studies can also address any other issues that may be identified by Panel based on their expertise.

Post-approval studies should contain a fundamental study question or hypothesis, safety endpoints and method of assessment, acute

and chronic effectiveness endpoints and methods of assessment, and a specified duration of follow-up.

The applicant did not provide a post-approval study plan or proposal in their premarket submission. If the device were to be approved, FDA believes a post-approval study is necessary because this is a permanent implant that is a first-of-a-kind device due to its combined toric and accommodative features. In addition, the premarket performance data does not reflect real-world device experience due to inclusion of highly selected centers and study population. Therefore, postmarket evaluation of device performance is needed to evaluate the real-world performance of the device, including device safety, such as vaulting concern, the long-term performance of the device, and evaluation of performance in subgroups.

The Panel will be asked to discuss if there is a need for postmarket evaluation of the real-world device performance, including the appropriate study question and study design, the safety and effectiveness endpoints to be included, the appropriate follow-up for long-term evaluation, and the need for evaluation of performance in subgroups. In addition, the Panel will be asked to consider these study elements, specifically for vault change, if this endpoint should be included in postmarket evaluation.

This concludes the FDA presentation, and I would like to thank you for your attention.

DR. HIGGINBOTHAM: Thank you, FDA, for your presentation.

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Just as a reminder, you do have about 10 minutes by our calculations in your presentation time.

Dr. Eydelman?

DR. EYDELMAN: Thank you. We can move on to Q and A.

DR. HIGGINBOTHAM: Okay. All right. I would like to thank all of the FDA speakers for their presentations.

Does anyone on the Panel have a brief clarifying question for the FDA presenters? Please remember that you do have time allotted this afternoon for additional questions, if necessary, as we do our Panel deliberations.

Any questions? Yes, Dr. Bradley?

DR. BRADLEY: Just a clarifying point. I think the FDA finished up its presentation really challenging whether or not the Trulign Toric Accommodation Posterior Chamber IOL actually provides one diopter of accommodation. The two statements were made earlier -- and I'll read one of them, it's from slide 14 -- it says, "The Trulign Toric Accommodation Posterior Chamber Intraocular Lens provides approximately one diopter of monocular accommodation." So the FDA made the statement twice, actually, and then questioned the Sponsor, so there was some confusion there, it seemed to me, in what the FDA was saying.

DR. EYDELMAN: Dr. Eydelman.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: So I believe the statements you were referring to were citations of the approved labeling of the parent IOL, and that indeed states that the parent IOL provides -- it was approved with the IFU of approximately one diopter for accommodation. That is correct.

DR. KIANG: Malvina?

DR. HIGGINBOTHAM: Yes?

DR. KIANG: Actually, the slide 14 was the proposed indications for use that is being brought to this Panel for discussion.

DR. HIGGINBOTHAM: Can you state your name, please?

DR. KIANG: Oh, Tina Kiang. Sorry.

DR. HIGGINBOTHAM: Dr. Bradley, did that satisfy your interest?

DR. BRADLEY: I think so.

DR. HIGGINBOTHAM: Dr. Bressler?

DR. BRESSLER: I had a couple of questions that came up in your analysis. The visual acuity outcomes, I presume, are for safety issues, and I noted that there were about 5 or 6% of the people who are missing between their Form 3 and Form 4. Did you carry forward the visual acuity outcomes and see what the results would be? I note, for example, there is one person with the toric 1.25 that's less than 20/40 at Form 3 and is missing at Form 4. I don't know if that's because it went away or is that the person who's gone.

So my question is have you looked at, either you or the

Sponsors, the missing data and what their visual acuity was at Form 3 so we can see if there were any safety issues that we don't have at their final follow-up?

DR. KIANG: Can you refer to which slide? I'm sorry.

Tina Kiang. Which slides are you referring to?

DR. BRESSLER: I'm referring to material that we were given by your Executive Summary.

DR. KIANG: Oh, the material in the -- I'm sorry -- Tina Kiang. The material in the Executive Summary, there may be an accounting, and we can check this for you -- the material in the Executive Summary was only data up to and including application data that was submitted until November 2012. Additional data from the final study report was submitted later.

DR. EYDELMAN: I don't believe that's Dr. Bressler's question.

DR. KIANG: Oh, okay. I'm sorry.

DR. EYDELMAN: We will check for you if that data was submitted by the applicant, and we'll get back to you after lunch.

DR. BRESSLER: Thank you.

DR. HIGGINBOTHAM: Thank you, Dr. Eydelman.

Any other questions? Yes?

DR. LEGUIRE: Larry Leguire. My question is referring to slide 53 and shows the number of reports received by year of adverse side effects, most of which are reported by the manufacturer. And whenever I see a

function like this, more and more lenses out there, more and more adverse side effects, which you would expect, and then in 2007, it peaked and it started to decline. To me, that seems counterintuitive, and I was wondering about what is going on here. Are the manufacturers simply not reporting the adverse side effects, or is something else going on to cause this type of function?

DR. EYDELMAN: So this is Dr. Eydelman. I believe you're referring to slide 53?

DR. LEGUIRE: Yes.

DR. EYDELMAN: That actually shows that in 2007, there was a peak of the reports of 309. As Maryam presented, there are lots of limitations to the MDR system, so we can only present the data as we found it.

DR. LEGUIRE: It's no comment, then, regarding the why or the incidence?

DR. EYDELMAN: Correct, no conjecture.

DR. LEGUIRE: Lenses are going up, incidence is going down. That, to me, seems very counterintuitive.

DR. EYDELMAN: Well, again, on slide 53, it shows in 2004 when the lens was first approved, there are 27 reports going up to 309 in 2007 to 156 in 2008, 183 in 2009, so from -- it's definitely up from 27 in 2004.

DR. LEGUIRE: But there's also 350,000 plus lenses out there

now is the issue.

DR. EYDELMAN: That's correct.

DR. LEGUIRE: We have these lenses going up and you have adverse side effects going down --

DR. EYDELMAN: And, again, I'd like to refer you to the slide that talks about --

DR. KIANG: Tina Kiang. Slide 50, please.

DR. EYDELMAN: Thank you. Slide 50 was a summation of well-established limitations of our MDR system. Unfortunately, the data we have is only as good as what's being reported to the system.

DR. HIGGINBOTHAM: Thank you, Dr. Eydelman.

Dr. Leguire, did you have any follow-up or --

DR. LEGUIRE: No. I just -- there's no easy explanation there, I think.

DR. HIGGINBOTHAM: Okay. Thank you.

Dr. Harris?

DR. HARRIS: This is David Harris. I think that germane to that question is -- the assumption, I think, is not correct, which is we are assuming that there is an increased frequency of implantation of these lenses over the years. I have not seen a table saying how many were implanted in 2004, 2005, 2006, but the -- if in fact we found that there were decreasing numbers of Crystalenses implanted over the latter half of this timeframe -- all we know

is that there's 315,000 over a 10-year period -- I think the chart I'd like to see is how many were put in each year and is that number going down?

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: And that would be something that you could ask of the Sponsor.

DR. HIGGINBOTHAM: Any follow-up, Dr. Harris?

DR. HARRIS: No, thank you.

DR. HIGGINBOTHAM: Any other questions from the Panel?

Dr. Coleman?

DR. COLEMAN: Anne Coleman. So on slide 82, where you have the distance corrected near visual acuity of 20/40 or better, I was -- the control subjects had 64.6%, and then the Crystalens study that was approved, I guess, back in 2003 was 90.1%. What's the ANSI standard? Has that been developed yet for that in terms of the distance corrected near visual acuity?

DR. EYDELMAN: Dr. Hilmantel?

DR. HILMANTEL: This is Gene Hilmantel. No. The ANSI standard has no target for that.

DR. COLEMAN: Okay.

DR. HIGGINBOTHAM: Okay. Is there a follow-up, Dr. Coleman?  
Any follow-up?

DR. COLEMAN: No.

DR. HIGGINBOTHAM: Okay. Thank you.

Yes, Dr. Clayton?

DR. CLAYTON: Janine Clayton. Back to slide 50, I know that Dr. Kiang mentioned that there are many limitations of the Medical Device Reporting system, including the fact that age and sex are often not included. Do you have any information at all regarding breakdown by sex at all, you know, taking into account the limitations?

DR. KIANG: Hi. Dr. Tina Kiang. The only information we have is that which was included in the reports.

DR. HIGGINBOTHAM: Is there a follow-up, Dr. Clayton?

DR. CLAYTON: Not at this time.

DR. HIGGINBOTHAM: Any other questions from the Panel members?

(No response.)

DR. HIGGINBOTHAM: I have a question. And this is based on the material that was sent to the Panel ahead of time. As I recall, a few of the protocol violations related to the methodology in terms of how patients were questioned related to their functional status, their subjective responses. And so the question is whether or not FDA found any differences in the responses of those patients that were in the pool that had those violations versus others. And, again, did you see any relationship between, you know, the age or even gender impact related to the functional status of the patients as they subjectively report?

DR. HILMANTEL: No. We did not request that type of analysis, and it was not provided to us.

So if I can just comment, the age and gender effects, those pertain to the analysis of the randomized group in terms of the effectiveness in treatment, so you have to understand, for example, for the gender effect, what's seen there is actually of -- even though the percents look large, the magnitude of the effect in terms of dioptic differences is small. For the randomized group, the intended correction was always 1.33 diopters. So if you're talking about a difference of 20%, that's on the order of .25 diopter for that group.

DR. HIGGINBOTHAM: Thank you.

Yes, Dr. Owsley?

DR. OWSLEY: That reminds me after looking also at the Executive Summary that you provided, what percentage in the clinical trial was the questionnaire administered, interview-administered, which was, I think, the protocol violation versus self-administered?

DR. EYDELMAN: Do we have that data available, or do you want to come back after lunch with that answer?

DR. HILMANTEL: I don't know off the top of my head. We can report back to you later on that.

DR. HIGGINBOTHAM: Any other questions?

Dr. Bressler?

DR. BRESSLER: Again, in the Executive Summary, I thought -- I don't have this memorized -- that the FDA requested data by age, which you showed, gender, which you showed, and investigators. And I thought that last one was important because I also thought in the materials that a large proportion of the enrolled subjects were by perhaps one investigator, which is a little unusual with nine sites from your slide 25. So I was wondering if you saw any unusual trends when you eliminated that one investigator from the overall results, granted, I know you're going to have small numbers, so the percentages start going all over the place for the primary outcome or for that single investigator.

DR. HILMANTEL: No, we didn't request that. I believe that the largest site was about 25% of the enrolled.

DR. BRESSLER: Okay.

DR. HIGGINBOTHAM: Any other questions?

Yes, Dr. Clayton?

DR. CLAYTON: Janine Clayton. Did you look at percent of intended reduction in absolute cylinder by both age and gender together, because I noted that -- I know that they're -- I mean, there are difficulties there, but if you look at the less than 60-year-old group, there's a reversal there, so I'd be interested in knowing whether women, for example, between 50 and 70 -- what that data might look like.

DR. LU: Yeah, that's a very good -- Laura Lu, statistician from

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FDA -- that's a very good question. For the treatment effect by age interaction, that's the one we are mostly concerned about. We did break up by gender, so we look at treatment effect by age in each gender group. So I would like to make a reference to a backup slide. It's page 50 in the backup slides --

DR. EYDELMAN: Panel members don't have backup slides, only FDA staff does, but we will be projecting it.

DR. LU: Yeah. So when we look at the treatment by age trend, in male, we see the similar trend, so you see the treatment decreases as age decreases in the male group. Next slide, please. We also look at that separately in female group, and the trends are the same. So it looks like the trend in treatment effect that decreases as age decreases is consistently shown in both female and male groups. Does that answer the question?

DR. CLAYTON: Yes. Thank you.

DR. HIGGINBOTHAM: Any other questions?

(No response.)

DR. HIGGINBOTHAM: I have a brief clarifying question. I understand related to the complication of vaulting and the issue of non-adherence, I noted, or as I recall from your presentation, you noted that early on in the postoperative period, the patient did have no flare and cell, suggesting that there was great adherence, but then later on, the physician concluded that it must be non-adherence that was related to the vaulting.

Was there anything else in the documentation that would suggest that the vaulting could have been related to anything but non-adherence?

DR. MOKHTARZADEH: The Sponsor -- oh, I'm sorry. This is Dr. Maryam Mokhtarzadeh. The Sponsor previously reported the appearance of capsular striae at some point in the postoperative period, but no, there was no additional information for me to make any conjecture about when that noncompliance could have occurred or whether there were any other contributing factors. We were really limited based on what the Sponsor and the investigator provided to us. But, again, the noncompliance was the conclusion of the investigator.

DR. HIGGINBOTHAM: This is Dr. Higginbotham following up. And did you say that that patient dropped out of the study as well?

DR. MOKHTARZADEH: Yes, that is correct.

DR. HIGGINBOTHAM: Thank you.

DR. MOKHTARZADEH: Or I'm sorry. Rather than dropped out, I should say was lost to follow-up. That was the correct terminology.

DR. HIGGINBOTHAM: Thank you.

Any other questions from the Panel?

(No response.)

DR. HIGGINBOTHAM: Going once, twice?

(No response.)

DR. HIGGINBOTHAM: Okay. Thank you. Thank you, FDA for

your presentation. And we are now ready for lunch. So, Panel members, please be reminded that you should not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We will reconvene in this room 40 minutes from now, and that will be at 1:15 approximately. I will ask -- is that the right time? Did I get that? Okay. Forty minutes, Dr. Eydelman, is that okay with you? Okay.

DR. EYDELMAN: Thank you.

DR. HIGGINBOTHAM: I will now ask that all Panel members please return on time. Please take any personal belongings with you at this time. This room will be secured by FDA staff during the lunch break.

Can we leave computers in the room, though? Yes? You will not be allowed back into the room until we reconvene. So everyone, bon appetit, and we'll see you at 1:15.

(Whereupon, at 12:35 p.m., a lunch recess was taken.)

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AFTERNOON SESSION

(1:18 p.m.)

DR. HIGGINBOTHAM: Going to call this meeting back to order.

The Food and Drug Administration will now give -- oh, nope -- we will now proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. Ms. Facey will now read the Open Public Hearing disclosure process statement.

Ms. Facey?

MS. FACEY: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For these reasons, the FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any company or group that may be affected by this meeting topic. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to

address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. HIGGINBOTHAM: All Panel members have been provided written comments received prior to this meeting and have had an opportunity to review those comments.

For today's meeting, each scheduled speaker will be given 6 minutes to address the Panel. We ask that you speak clearly to allow the transcriptionist to provide an accurate transcription of the proceedings of this meeting.

The first speaker is Dr. Daniel Goldberg from Atlantic Eye Physicians, and he will be followed by Dr. James Davies from Davies Eye Center, and finally, Dr. Jonathan Solomon from Solomon Eye Physicians and Surgeons.

Dr. Goldberg?

DR. GOLDBERG: Madam Chairman and members of the IRB Panel, good afternoon and thank you for this opportunity to address the application for the Trulign lens.

I am a customer of Bausch & Lomb, not a consultant, and have no financial interest. I am also a clinical ophthalmologist from New Jersey with a subspecialty in cornea cataract and refractive surgery. I have been involved in clinical research on the surgical correction of presbyopia and have developed a computer-animated model of accommodation along with the

theory of reciprocal zonular action to explain the mechanism of accommodation.

I hope that my theory of reciprocal zonular action will help in the further development of intraocular lenses and other surgical approaches to the correction of presbyopia.

In my surgical practice and for the benefit of my patients, I prefer the Crystalens for achieving the best quality of vision for patients who choose a presbyopia-correcting lens. I also have elected to have Crystalens for my own cataract surgery and would like to share my experience with this lens. In addition, I have preexisting astigmatism as well as postoperative astigmatism still present in the same axis and magnitude following Crystalens implantation in both of my eyes. I hope to have femtosecond laser arcuate keratotomies performed to further improve my uncorrected vision.

At present, I enjoy spectacle-free vision over 90% of the time, and the ability to see at all intermediate depths is phenomenal. I currently wear spectacles for my far distance vision, when driving, especially at night, and to correct for extended near vision with small print.

With the initial surgery for cataract, there was a medical necessity to proceed irrespective of the choice of lens. I had cataracts, and I needed to see better. A secondary procedure for astigmatism is now under consideration to improve my freedom from glasses especially for distance, but this is tempered by the concern that astigmatic keratotomy even with the

femtosecond laser could yield a disappointing visual result and possibly produce unwanted symptoms such as glare or foreign body sensation in the setting of dry eye syndrome, which is common and which I also have.

In current practice, an astigmat with cataract who chooses Crystalens may require two or even three procedures to achieve their final result. There would be the initial cataract surgery with intraocular lens implant, often followed by YAG laser capsulotomy, and finally an astigmatism procedure.

I would also point out that some patients are better served with a lens-based solution for astigmatism compared with corneal procedures like LASIK or astigmatic keratotomy. Clearly, a more efficient procedure is needed.

With respect to other presbyopia-correcting lenses, the alternatives to Crystalens which are FDA-approved are all multifocal lenses. It has been well established that multifocal lenses reduce contrast sensitivity, and patients more frequently report disturbing symptoms such as waxy vision, glare, and halo. Patients with multifocals occasionally demand lens exchange due to unacceptable quality of vision and disturbing side effects. These eyes are exposed to considerable risk when IOL exchange is needed, not to mention additional cost to the taxpayer.

Multifocal lenses are generally not recommended in the presence of corneal or retinal disease. However, we cannot predict whether

a patient in their 60s, such as myself, will develop corneal or macular disease 15 or 20 years later. As a cataract patient, I feel that my choice of Crystalens protects me from adverse consequences that could occur if I chose a multifocal. As a cataract surgeon counseling patients, I prefer not to recommend multifocals because of both near-term and long-term risks.

I have reviewed the data in the Trulign application, and I encourage the Panel to approve it. The configuration of the haptics make the lens particularly well-suited for stable fixation, reducing the risk of rotation. It would be especially disappointing if American eye surgeons had only multifocal astigmatism correcting lenses and could not choose Trulign to address coexisting astigmatism. Had Trulign been available when I needed cataract surgery, very likely, I would not have to face an additional procedure now.

Thank you very much.

DR. HIGGINBOTHAM: Thank you, Dr. Goldberg, for your comments.

We will now invite Dr. Davies to the podium. You have six minutes.

DR. DAVIES: Thank you very much. It's a pleasure to be here. I appreciate the opportunity to address the Panel. And I'm grateful to Dr. Goldberg, too, for that insight that he provided.

I am a paid consultant for Bausch & Lomb Surgical and am here

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at their invitation and support, but even without that would have come. I have had nearly 11 years now of experience with the Crystalens, and it began with reading an article in *Ocular Surgery News* back in March of 2001, where Stuart Cumming, the inventor of the Crystalens, described experiences he'd had using the STAAR plate haptic lens. The patients seemed to be able to accommodate, and that was surprising, as this certainly was not designated that. And I had noticed the same thing, but attributed it to a miotic pupil, increased depth of field for that reason. But as I read this article, I instantly knew that it would work. And I called Stuart on the phone and said to him, "I believe you're on to something." And he assured me that he was on to something.

So my interest began at that point, and I wanted in. I wanted to have access to this technology. So about a month after FDA approval in 2003, I implanted my first implant in December of 2003 and have subsequently had experience with all of the Crystalens models, including being involved in some of the studies. I apologize, some of the dates may not coincide with what you have. I did these from memory. But the AT50, for example, I believe, was in 2007.

This is a letter I sent to Dr. Cumming. "Dear Stuart, I wanted to share with you again how thrilled I am with the way your great work with the Crystalens has made my career so much more fulfilling than it would have otherwise been. Each time I finish a procedure that I know has been done

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correctly, I know I'm going to have a really happy patient who sees better than me. That is both very annoying, in some respects, and very gratifying. Thanks so very much for improving the lives of so many."

Now, things that we've learned along the way, and it's been immensely helpful to be able to consult with colleagues who have also had experience, and I think we've learned how to make this work and how to make it work better: biometry critical; a well-centered anterior capsulotomy of just the right size so that the symmetric coverage of the haptics is essential; meticulous cleanup of the cortex in polishing the interior and posterior capsule as Dr. Packer pointed out earlier; and then rotating the lens to the best fit position.

This, of course, is going to be critical to capsulotomy in the implantation of at Trulign Toric. And as one of the clinicians involved -- I believe we had 21 of the eyes included in this study -- that's something that we, of course, confirmed. A watertight incision is absolutely critical. And one final step involves when it looks like the surgery is completed, and since going from a suture, this has become much easier -- I haven't used a suture for several years now -- but I like to go in with the I/A tip and do one final rotation dialing of the lens or at least partial rotation just to be sure that it is, in fact, situated in the equatorial capsular bag.

The Crystalens patients are extremely happy with the results. They have a seamless range of vision. I've found that pilots, for example --

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living in San Diego, we have a lot of retired military pilots. They are jet jockeys, as they call themselves, who then moved on to careers with the airlines. These pilots started showing up, one after another after another, because word got out that with this Crystalens, not only can you see incredibly well at a distance, but you can see the instrument panel, you can read. And that's one group that has been very, very happy with it. The results are predictable, they're stable when the proper surgical protocol is observed. And significant spectacle independence is typically achieved.

To Dr. Leguire's point earlier that it seems the complication rate was going down, I believe that's true. That's what we've experienced in San Diego. I've tried to be very open with my colleagues, encouraging them to use that, and those who follow the protocol correctly do, in fact, have excellent results with it.

My experience with the Crystalens AO, which is my preferred lens at this point, is very good. If I had cataracts, I would certainly choose the Crystalens or the Trulign Toric, as needed. My father-in-law has a Crystalens. I'm flying home to San Diego today. I'm going to be operating on my brother tomorrow. I love my brother. I love my father-in-law. And my brother is getting a Crystalens. He has no idea how much it costs, so I get to pay for it.

I have one patient, a psychiatrist, and this is what he said to me. "If an ophthalmologist does not inform a patient of the availability of and result of Crystalens, in my opinion, he's guilty of medical malpractice." I

don't know if I'd go that far, but I do think that it's very appropriate that our patients understand that this is a possibility. He's thrilled that he can speak to his patients, he can look in their eyes, he can write his notes, and now he's into electronic medical records, without having to put his glasses on, and he's very symbolic of the kinds of results we've had.

Thank you very much.

DR. HIGGINBOTHAM: Thank you, Dr. Davies.

And finally, Dr. Solomon, we invite you to the podium. Is Dr. Solomon here? I don't see Dr. Solomon coming to the podium.

Does anyone else wish to address the Panel at this time? If so, please come forward, and you'll have three minutes to provide testimony.

(No response.)

DR. HIGGINBOTHAM: Okay. And do any of the Panel members wish to ask any of our speakers questions? We do have time for that.

(No response.)

DR. HIGGINBOTHAM: Seeing no hands raised, we can now proceed to the next section.

I'd like to once again thank our two speakers for their presentations, and certainly, their presentations will help our deliberations, I'm sure. So we appreciate their time and effort in coming here.

I now pronounce the Open Public Hearing to be officially closed, and we will not take any additional speakers at this time.

Okay. Would any of the -- we already asked you if you wanted to ask any of the public hearing speakers a question at this time, so -- okay.

Now we will proceed with Panel deliberations. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This, of course, helps the transcriptionist identify the speakers.

Okay. So is the Sponsor prepared to respond to Panel questions from this morning? Were there any -- oh, yes, FDA? So the FDA is at the podium now.

DR. KIANG: We are prepared to address the three -- the two questions from this morning and to clarify the answer to one of your questions from this morning.

DR. HIGGINBOTHAM: Okay. Thank you. Would you like to state your name?

DR. KIANG: Tina Kiang. Thank you. Hi, Tina Kiang. I believe Dr. Bressler asked a question about a visual acuity outcome regarding one subject at Form 3 and how they were followed until Form 4. I believe that that information is -- you referenced was in table 13 of our Executive Summary. I'll let Dr. Gene Hilmantel answer the question.

DR. HILMANTEL: Okay. Gene Hilmantel. So I mean, I think the slide pretty much addresses the question here. At Form 3, there was one eye

that had corneal edema, and that was resolved, and the eye later achieved 20/25 acuity.

DR. BRESSLER: Thank you.

DR. KIANG: Tina Kiang. The second question was regarding the subject questionnaire and the deviations regarding the subject questionnaire and whether they had any effect on the outcomes.

DR. MOKHTARZADEH: So we just wanted to clarify here that at one site, there were 19 subjects for whom the study coordinator read questions to the subjects, and at one site, there were 10 subjects for whom a source worksheet was provided, and then a study coordinator later transcribed the results over to the case report forms.

DR. KIANG: Dr. Tina Kiang. And Dr. Hilmantel wanted to clarify the question -- and we don't remember who asked the question -- I'm sorry -- regarding the number of sites at one particular -- number of subjects, excuse me, at one particular site.

DR. HILMANTEL: Gene Hilmantel. I think maybe Dr. Bressler asked this question also. So there was -- I misspoke earlier. There was one site that had 68 subjects and that represented about 30% of the total enrollment. The protocol called for no more than 25% of the total toric implanted subjects to be at any one site. And that site did have 25% of the toric implants.

DR. BRESSLER: Neil Bressler. So did you analyze the data

without that site and look at the data just from that site to see if there was a large discrepancy? I know you can't rule out a moderate or small discrepancy when you're doing that.

DR. HILMANTEL: And we didn't specifically ask for that, but the results were reasonably consistent across sites.

DR. BRESSLER: Okay.

DR. EYDELMAN: I believe that completes the outstanding questions we had from this morning.

DR. HIGGINBOTHAM: Did the Panel have any additional questions for FDA before they leave the table? Yes, Dr. Leguire?

DR. LEGUIRE: I'm very curious about the haptic break you said occurs with these and as well as other intraocular lenses. And given the stress characteristics of this particular lens with accommodation, you'd expect -- as the company demonstrated, they looked at the stress features of a lens by vibrating it by 10 Hz for a million cycles, something like that, I remember in their literature. And is that about right? And I was curious, given this, in the long-term, you'd expect perhaps these -- the failure rate of these lenses to increase with age. And I was just curious if there was any data from the manufacturer or FDA regarding the haptic breakage in these types of lenses compared to the monofocal lenses.

MR. CALOGERO: Yes. There's a lot of preclinical testing that's involved, and there's stress analysis that cycle through at least a quarter-

million cycles. We have shipping tests. We look at transport testing. We look at shelf-life. So there's a lot of testing that's done to assess any sort of breakage of the haptics. We have simulated injection of the lens to the injector, and typically, the company needs to demonstrate that there is stability and there's lack of breakage of the haptics. But when it goes out into the real world, that's invariably what we see when the MDRs, you do see haptic breakage. And it could be from the surgeon putting it in the injector a little bit incorrectly. It could be subjected to stresses way beyond what was anticipated in the shipping study. But it is a common feature you see associated with IOLs.

DR. LEGUIRE: And I'm sorry. My basic question is the ones with accommodative IOLs greater than that of the non-accommodative, or you know, just the fixed?

MR. CALOGERO: Based on what I saw there in that slide, I would say no.

DR. LEGUIRE: Okay.

DR. HIGGINBOTHAM: Okay. Any other questions for FDA before they leave the table?

(No response.)

DR. HIGGINBOTHAM: Thank you, FDA, for your --

DR. BRESSLER: Oh, I have one --

DR. HIGGINBOTHAM: Oh, one more question, Dr. Bressler?

DR. BRESSLER: I do want to get this from the Sponsors as well, but just to get the FDA's perspective -- so for the primary endpoint of percent reduction in cylinder, could you discuss how reliable that is, and because we don't have masking of the people who are making that measurement, whether there's any chance for bias inadvertently or otherwise when those measurements are being made?

DR. HILMANTEL: So the percent reduction is -- you're right. I mean, it conceivably can be subject to bias because the results are based upon the manifest refraction. So you're correct, but we haven't noticed a particular problem with that over the course of different toric IOL studies, but that is a potential problem.

DR. BRESSLER: Thank you. This is Neil Bressler. So I'll come back just to clarify with --

DR. HIGGINBOTHAM: Okay.

DR. BRESSLER: -- the Sponsors when we get to that. Thank you.

DR. HILMANTEL: Yeah. Just one more comment. The manifest does partially explain the age effect, the issues with the manifest. The control group -- when we looked at the data, the control group had for younger patients, there was more of a difference between the manifest and the keratometric cylinder than for older patients.

DR. HIGGINBOTHAM: Okay. Thank you. Do you have an

explanation for that difference? This is Dr. Higginbotham.

DR. HILMANTEL: Well, I think it's difficult to explain. As all the clinicians know, manifest is done sort of in a variety of ways by different practitioners and different technicians, and so it's subject to many factors that we don't have really a handle on.

DR. HIGGINBOTHAM: Dr. Steinemann?

DR. STEINEMANN: I may have missed this, but with respect to the accommodative performance of the lens, was there any breakdown in how the lens performed, the movement, the accommodative ability with respect to how long it's been in the eye after implantation?

DR. HILMANTEL: Yeah, we don't have data on that. Maryam, Dr. Mokhtarzadeh, mentioned the one study by Marchini where he made measurements at one month and at 12 months. And so in that single study, there was decline over time, but we don't really have solid data on that.

DR. HIGGINBOTHAM: Thank you.

Dr. Feldman?

DR. FELDMAN: Yes. Was any data submitted regarding the difference in age and the intended astigmatic correction based on how much surgically induced astigmatism there was by age?

DR. HILMANTEL: No.

DR. HIGGINBOTHAM: Yes, Dr. Tarantino?

DR. TARANTINO: Nick Tarantino. The question I have is just for

a better case of my understanding -- is the questions relative to the accommodation. It was my understanding that the design of this study was really primarily to address the correction of residual cylindrical -- the reduction of residual cylinder. Was there discussions up front with the Sponsor that they would have to demonstrate accommodative amplitude, because if there were, I would make the presumption that the study may have been designed a little bit differently than it currently was?

DR. EYDELMAN: So I'll take that. Malvina Eydelman. As Maryam mentioned several times in her presentation, the original study design was based on the presumption that the toric addition to the parent IOL will not change the accommodative ability of the new lens. So it was that and the lack of accommodative standards or guidance at the time, the Sponsor proceeded with the design of this study as you saw. Having said that, I believe on slide 31, Maryam brought to the Panel's attention that applicant was advised that in the future PMA application for the approval of the toric modification, they would be asked to address issues related to accommodative effectiveness that had been raised in the literature.

So you're correct. It was not done at the original. But, again, the parent IOL was approved in '03, and the first standards got together in '04. And as you well know, the data available about accommodation and what it is that's needed to assess a new accommodating IOL has been evolving significantly in the last decade. Hence, we are where we are today.

DR. HIGGINBOTHAM: Dr. Tarantino, do you have a follow-up?

DR. TARANTINO: No, not at this time.

DR. HIGGINBOTHAM: Okay. Any other questions -- oh,  
Dr. Bradley?

DR. BRADLEY: This is really a comment to the FDA. You presented the ANSI Z80.30 toric IOL standards I presume we've been working on, and the outcome measures are reduction of cylinder and lens axis misalignment. And I recall between myself and the FDA, we've had this discussion multiple times about the importance of doing a full vector analysis of any toric lens. The reasons are well known. And, for example, this provides a useful outcome measure, I think, for performance, but it doesn't allow you to examine what went wrong; did the lens misalign or was it the wrong power. And if you do a full vector analysis, you'll learn that, and that can help make recommendations to Sponsors; do you need additional powers, do you need better control of axis. All that can come from the vector analysis, and it would be nice to see that somehow creep into a standard, if possible.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: Yes, Dr. Bradley. We perfectly agree with your assessment. And if you look at slide 7 of our presentation, it says that while a toric IOL standard has been completed, it is awaiting FDA's recognition. Now, during the recognition process, we can add or delete a requirement that we

do or do not agree with the standard, i.e., an ANSI or an ISO standard are not an FDA document. And in the process of recognition, we would call upon clauses which we believe need additional work or at different outputs than we agree to.

DR. HIGGINBOTHAM: Any other comments? Dr. Bradley, any follow-up on that?

(No response.)

DR. HIGGINBOTHAM: Any other comments or questions for FDA? Yes?

DR. HILMANTEL: Yeah. Gene Hilmantel. I just want to address that briefly. We have had submissions in which the vector analysis was done to help assess alignment of the toric IOL. And those assessments were not found to be very helpful. With the development of the newer methods of objectively measuring the axial alignment, the image capture and alignment to the ocular features, those assessments of axial alignment are much more accurate and repeatable than the assessments based upon the manifest refraction. We did have assessments of vector analysis -- we did have vector analyses of the results of the surgically induced astigmatism. So that was used to assess the effects of that.

DR. HIGGINBOTHAM: Dr. Bradley?

DR. BRADLEY: Yeah. Just a follow-up. I think Gene's right here, that the photographic techniques can give you tremendous accuracy.

At issue, though, is whether or not in the end everything aligns with the refraction. So the refraction becomes the ultimate test of how everything lined up, whether it be if you're using corneal topography or some anterior corneal surface measurement to assess your reference axis. You've not included the posterior corneal surface, for example. All of that adds up to produce the final refractive astigmatism. So I think there's still benefit even though the accuracy or precision may not be as great for the refractive outcome as it would be for the photographic outcome. I think the value of it is still to be considered.

DR. HIGGINBOTHAM: FDA, any follow-up comment? Gene?

DR. EYDELMAN: Thank you for your comments.

DR. HIGGINBOTHAM: Okay. Seeing no other hands raised, thank you, FDA, for responding to our questions. I would like to invite the Sponsor back to the table once FDA leaves the table for additional questions from the Panel.

First of all, Sponsor, do you have any comments you'd like to make in reference to any of the questions from the previous session?

MS. McEACHERN: Not at this time.

DR. HIGGINBOTHAM: Panel, do you have any questions for Sponsor at this time? Dr. Bradley, then Dr. Bressler.

DR. BRADLEY: I have a very simple question. In your presentation, and the FDA mirrored this, we talked about this being a pivotal

study. That kept coming up. Could you tell me why it's pivotal? The word was used many times.

DR. HAYASHIDA: This is Jon Hayashida, Bausch & Lomb. The trial as utilized is a Level B-like study to an approved parent IOL to establish the safety and effectiveness of the addition of a toric optic to the approved parent platform to evaluate its ability to reduce, you know, refractive cylinder.

DR. HIGGINBOTHAM: Any follow-up, Dr. Bradley?

DR. BRADLEY: Yeah, that's what I thought the study was, too, and that's why I wondered about the word pivotal, but it sounds like we agree except on the word.

DR. HIGGINBOTHAM: Dr. Bressler, you had a question, and then Ms. Berney.

DR. BRESSLER: So just to follow up the questions I had with the FDA, and for any one of you, the first is on the potential for bias when measuring that primary outcome. Could you just walk us through how the primary outcome was measured again, briefly, and whether you think there's any potential for bias if that person doing that measurement was not required to be masked?

DR. HAYASHIDA: Jon Hayashida, Bausch & Lomb. The primary measure measured the resultant manifest refractive cylinder against the preoperative delta k against the intended correct, which was calculated by

the toric calculator. So all surgeons were -- I mean all sites were trained in refractions, but they all had to be trained optometrists, ophthalmologist, or a trained technician, and in collaboration with the FDA. Following international standards at the time of the protocol approval, this was not a requirement.

DR. PACKER: Mark Packer. If I might just add one small point to that, which is that when a manifest refraction reaches a 20/20 visual acuity, I think that that tends to eliminate any potential bias, and the best corrected visual acuity in both groups is equivalent and approximates 20/20.

DR. BRESSLER: And then the other question, again, because you want to potentially -- maybe this is a pivotal study because you want to get it for approving an indication. So I think about things that could potentially affect that. And so again, that's why I was asking about the site that had 68 subjects enrolled because you often try to avoid that in case there's some systematic unknown bias by a particular site. So have you looked at the data of that individual site or the data without that and seen any differences in the outcomes to suggest there may have been some unknown bias in the results that we're looking at?

DR. HAYASHIDA: Jon Hayashida, Bausch & Lomb. No, we did not look individually at that site's outcome or look at the outcomes with that site removed.

DR. BRESSLER: Neil Bressler. Thank you.

DR. HIGGINBOTHAM: Ms. Berney?

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MS. BERNEY: Barbara Berney. This has not come up yet, but it is especially near and dear to my heart because I am a refractive surgery casualty. I have also had bilateral cataract surgery. And I know how difficult, because I deal with people who are casualties all the time who now are approaching the age of cataract -- the necessity to have cataracts removed. Many of them have had very poor outcomes from IOL implantation. And my question is in the patient information brochure, it states that people who have had prior corneal refractive surgery, for example, LASIK, are acceptable candidates for implantation as long as their eye is in good health. If you've had already cataract surgery, you are not a candidate. However, one of the exclusion criteria for this study was previously corneal refractive surgery, so that would tell me that there weren't any people like me in your study. So my question is how can you claim that it's good for them if you didn't have any of them in the study?

DR. PACKER: This is Mark Packer. Patients who've had LASIK such as yourself represent a unique and special population particularly at the time of cataract surgery. And there are increased risks and an increased level of difficulty in achieving a good result in those patients. These include problems such as dry, irregular corneal astigmatism and significant challenges in attempting to calculate the correct intraocular lens power to achieve a good visual result.

Given all of these difficulties and challenges, in general,

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Sponsors who are seeking approval for a new product before the FDA limit the population to healthy eyes of healthy patients to avoid unnecessary risk during the clinical trial process. Unfortunately, the outcome is a limited amount of data for the FDA to review for patients who have a history of corneal refractive surgery.

DR. HIGGINBOTHAM: Follow-up?

MS. BERNEY: Yes. My question is how can you claim that it is safe and effective for those people if it hasn't been tested in them?

DR. PACKER: Mark Packer. As far as I know, I don't believe the Sponsor is seeking a labeling claim for patients with a history of keratorefractive surgery.

MS. BERNEY: In the patient information brochure on page 10, it clearly states that people who have had prior corneal refractive surgery, for example, LASIK, are acceptable candidates for implantation as long as their eye is in good health.

DR. PACKER: Well, if I may, my own clinical experience would support that. I have had good results with the Crystalens in post-LASIK patients, and I actually believe it's a better solution for LASIK patients than, for example, a multifocal lens would be. So my own clinical experience supports that.

DR. HIGGINBOTHAM: Ms. Berney, you have a follow-up?

MS. BERNEY: I do. I have to say I'm quite surprised to hear

that because the patients who seek our help, most of the people who come to us have had very poor results from LASIK, so their corneas are very aberrated. Their vision is unacceptable. If they have cataract surgery, if it's off even a little bit, it makes their lives more miserable. So .25 diopter might not seem like a lot to somebody who has perfect virgin corneas, but if you've had previous refractive surgery and it isn't quite what is expected, it can really make a huge difference.

Furthermore, many of the surgeons who do this cataract surgery on former refractive surgery patients do not understand very well how to calculate those measurements. So, for instance, I have a patient who is 4 diopters off. She can't have any more refractive surgery because her corneas are too thin. She cannot wear contact lenses because she is the queen of dry eye. What do you do for somebody like that? So I'm concerned that saying that it's -- if you haven't tested it on anybody -- and I have astigmatism, residual astigmatism, a lot of it. I know how difficult it makes my life. I can't imagine telling somebody this is safe for you if you haven't tested it on anybody who has had those kinds of problems or who has had refractive surgery. If it's specifically excluded from the study, I don't know how you can say that you can do it on those people.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: I just wanted to clarify that the proposed patient and physician labeling that was posted is what's currently proposed

by the Sponsor. It's not something that has been reviewed or approved by FDA. Should the device be found to be approvable, then the labeling will undergo FDA review and will be modified per FDA's recommendations.

DR. HIGGINBOTHAM: Thank you.

Dr. Harris?

DR. HARRIS: In reference to the question that Dr. Leguire and I posed earlier, actually, when the FDA people were up there, can you present the year by year data of the numbers of Crystalenses implanted per year over the last decade?

MS. McEACHERN: Denise McEachern, Bausch & Lomb. We went back and looked at our sales data, and what we're able to tell you is that the sales of the Crystalens IOL shows a similar trend to that of the MDRs that were reported by FDA on their slide. Beginning in 2004, there was an increase in sales through 2008, peaking in 2008, with a slight decrease in sales after that to the present day. So the overall sales mirror the MDR reporting.

DR. HARRIS: Thank you.

DR. HIGGINBOTHAM: Follow-up, Dr. Harris?

DR. HARRIS: Thank you.

DR. HIGGINBOTHAM: Okay.

DR. HARRIS: I think that that, to me, says that the rates of these complications we're looking at, the ones that are resulting in

explantation and lens tilt and everything has probably -- it's not been solved, but either surgical techniques or design modifications -- if it's parallel, those instance may be -- now, we can't know for sure the denominator, but it sounds like it -- nothing that has that many big changes there. We don't expect them to be necessarily better or worse.

DR. HIGGINBOTHAM: Any other questions?

Yes, Dr. Owsley?

DR. OWSLEY: I just had a question -- maybe you presented the data like this, but I just didn't see it. For example, if we look at uncorrected near visual acuity, what percentage of those in the Trulign group versus the controls achieved 20/40? I don't mean 20/40 or better, just 20/40. In other words, I'm trying to get a handle on the distribution of visual acuity. I realize you're expressing it as 20/40 or better and that's the outcome, but I'm trying to get a feeling for, for example, for near visual -- uncorrected near visual acuity or uncorrected distance visual acuity, what percentage of the sample, that's all they could achieve is 20/40?

DR. PACKER: And this is Mark Packer. On my slide 33, which is -- was part of my presentation this morning, I showed the distribution of uncorrected near visual acuity for the effectiveness cohort. This includes all eyes implanted with one of the three powers of the Trulign Toric Accommodating IOL.

DR. OWSLEY: So about 33% of the sample could only achieve

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20/40; is that correct? Am I reading that right?

DR. PACKER: This is Mark Packer. Right. So 33% achieved 20/40; 20% achieved 20/32; 13.5 achieved 20/25, and 3.8 achieved 20/20. And then on the worse than 20/40 side, you can see the distribution there.

DR. OWSLEY: Right. Okay. So how about the equivalent slide for uncorrected distance visual acuity? Do you have that?

DR. PACKER: Well, I don't have it formatted quite like this. Just to go along the same line, the very next slide, or the slide just before this one, one or the other, shows the intermediate, which may be of some interest to you, and we can show that slide here, intermediate visual acuity, put that one up for you, with the mean of 20/20, but really 40%, little over 41.5% right at 20/20, and then you can see the distribution there.

I don't have a slide in this exact same format for the distribution for uncorrected distance. However, it is in the Executive Summary, there's a listing of frequency distribution, so is it 20/20 or -- cumulative distribution, so it's 20/20 or better; 20/25 or better; 20/30 or better. So you can subtract to figure out the same numbers.

DR. OWSLEY: Sir, my question is let's focus on the near and the distance because that's what the slide was -- you had. To what extent would you say that the Trulign is allowing for near, intermediate, and distance vision without spectacles for some 30% of the patients? There's many visual tests that you need better than 20/40 for distance. For example, road signs,

according to federal standards are designed for 20/30 or better. And, certainly, if you're trying to read a font from a phone book or if you're even reading on a computer, you need better than 20/40. So I guess I'm trying to get at what is really meant by -- allows for near, intermediate, and distance vision without spectacles? Doesn't it depend on what you're doing?

DR. PEPOSE: Jay Pepose, medical monitor. Well, I think you're absolutely right, but I would point out that the data that we've shown here are monocular data. In the studies that I've published now with the parent model, the five-o and also the AO model, we found that by binocular summation, we've gained at least a line at near vision, so binocularly 20/40 becomes 20/30 at near. We've also asked those patients in those studies what their spectacle independence was, and it was very substantial. We had 43% of patients who said they never wear glasses either for sustained reading tasks or for short reading tasks. So I think that we shouldn't translate the monocular data into real world because these patients are all implanted binocularly in the real world.

DR. OWSLEY: Well, I might follow that up with that you're assuming that the other eye, which if it was implanted, was as good as or better. But in the case where it's worse, actually, there could be binocular inhibition and the vision would even be worse. So it could go either way, would you agree?

DR. PEPOSE: I would agree. And I think that's why most

surgeons in the real world implant the first eye and then target the second eye based on the first.

DR. HIGGINBOTHAM: Thank you, Dr. Pepose. Yeah, Dr. Brown?

DR. BROWN: Yes, Jeremiah Brown. I just wanted to come to that very small group of seven patients who are under age 60 and just hear your thoughts about that. I mean, in looking at the data, it's not only that that group didn't get as much astigmatic correction as we would have expected, but also the control group seemed to get a better result than would have been predicted. And were there any outliers or any -- did you look at those seven patients and see, you know, one patient in each group drive all the data to become -- have a such a wide distribution or --

DR. HIGGINBOTHAM: Sponsor?

DR. PACKER: This is Mark Packer. Looking at the age effect, the first thing you'll notice, and you pointed out, is that really, the effectiveness of the toric is about the same across all the age groups, and in the slides that FDA presented this morning showing those two lines which sort of intersected at about the age 60 and a little younger for the women in the study, the line for the toric is actually relatively flat. It's the line for the control which is angled. And so what we're really seeing is that the young patients in the control cohort had unexpectedly good correction of their astigmatism. Now, we know there are some variations in astigmatic axis, for

example, by age and other effects, such as that, which may play into this sort of increased, unexpected effectiveness in the reduction of cylinder by those -- and, again, it was a small number of 11 eyes -- but those in the control group rather than any difference, actually, in the percent of reduction achieved in the toric group.

DR. HIGGINBOTHAM: Any other questions for -- yes, Dr. Feldman?

DR. FELDMAN: Yes. Coming back to that idea of some of these smaller groups of patients with the study who had unexpected changes in their astigmatism, when you presented the data looking at the percentage of patients who ended up within .50 diopters and 1 diopter of intended astigmatic correction, the numbers were quite good. But there were about 18% of patients who were not within .50 diopters and another 4 to 4.5% who weren't within a diopter. Do you have any explanations for why that happened? This is all within the randomized 1.25 diopter group. And I know that vector analysis was not used or is not submitted, but was that performed on those subset of patients?

DR. PACKER: So this is Mark Packer. I'd like to, in regard to your last point, echo what Gene Hilmantel said, which is trying to do that vector analysis based on the manifest refractive cylinder postoperatively, there's a lot of noise. And clinically, you'll know this, because when you have people who have .25 or .50 diopters of uncorrected cylinder and you're

prescribing glasses, the precise axis of that small amount of cylinder may vary depending on which image they say is better, one or two. And even in the hands of a skilled, unbiased refractionist, there tends to be a lot of noise. And when you back calculate the intended alignment, or the calculated alignment of the IOL, based on the postoperative manifest refractive cylinder, you get wildly varying positions of the IOL, which you know are not true because you've got the photographs to prove exactly where the IOL is. So that's why that vector analysis was difficult and didn't help.

There are, to address the first part of your question, a small number of subjects, you know, who did not achieve within that .50 diopters or 1 diopter range. And the one thing we do know very clearly is it's not due to axis misalignment. You know, the axis misalignment results, I think, are the cleanest, sharpest data we have in this whole study because it's digital photography sent to a reading center, and they're just lining up conjunctival landmarks and drawing lines, and there are little marks on the IOL, and there's just -- it is what it is.

So that much we can say certainly, but we know as cataract surgeons we're dealing with a living, you know, biomechanical tissue, which has a variety of wound healing responses, et cetera, and I think that explains -- if you look at the, specifically the surgically induced astigmatism, we'd like to believe it's .50 diopters in every case, but in fact, in every study that I've reviewed, and in this study as well, there's a rather large standard deviation

in terms of surgically induced astigmatism. And within sort of the standard practice today of basing our IOL selection on preoperative keratometry, you know, we're not going to get any more accurate than this.

DR. HIGGINBOTHAM: Yes, Dr. Bradley?

DR. BRADLEY: Just a follow-up on the vector analysis. The point you make is completely correct. The important thing to realize, though, is that if you do the vector analysis, you will reveal how insignificant these wild axes are that you can get. And I'll give you an example. An example would be if you had a perfect toric correction, you had one diopter of astigmatism to correct, you put in a one diopter toric correction, but it was just off axis by 1 degree, the resulting astigmatism would have a 45-degree difference in angle. You get a very large change. But the amplitude of it would be tiny. And that comes out naturally from the vector analysis. And then you can do statistics on that to assert that, in fact, this is insignificant. So it's a tremendous value to you, I think.

DR. HIGGINBOTHAM: Yes, Dr. Harris?

DR. HARRIS: Just a comment on some questions of yours earlier, Dr. Brown, as to why in the absence of vector analysis that the younger group, you know, seemed to have unusually -- at least not -- it's hard to document the difference between the study and the control group, but besides, as you mentioned, surgically induced astigmatism, younger people are going to, you know, you would think would have maybe a little more

robust wound healing. They might not get as much flattening in the axis of the surgical incision. They may have more capsular contracture and proliferation, and this could induce some lens tilt or slightly different positions of the lens, which -- and I have not seen analysis of that, but there's a lot of things that in that small number, in that younger group, actually don't bother me that much because of those other factors which could mean there was -- and I really think that the stability of the IOL is certainly the key thing we have to look at here, and I think they -- in my opinion, that looks pretty good.

DR. HIGGINBOTHAM: Any other questions for Sponsor?

Dr. Feldman?

DR. FELDMAN: Just to follow up. So certainly the stability was excellent, and on most of the patients, you got what you intended. The reason I wanted to focus on those patients that were 1 diopter or more off or .50 diopters off is, often, with the current IOL technology that are torics, those patients, you may go back in and adjust the position of the lens. I noticed in this study that there were no lenses that there were repositioned. And I didn't see if there was criteria for repositioning other than misalignment from the photographed axis. Has there been any experience that you know of of repositioning these lenses to change the axis and the success of that?

DR. PACKER: Mark Packer. There was no significant lens axis

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misalignment in this study. The mean was less than 2 degrees. The mean from target was less than 5 degrees. And so we had no rotations due to misalignment.

DR. HIGGINBOTHAM: Any other -- yes, Dr. Bradley?

DR. BRADLEY: This is Dr. Bradley. Following up on Dr. Owsley's question really about the spectacle use at near, there are some fairly interesting issues to consider, I think, there. First off, if we look at the presbyopic population, at what point do they require a reading add? Typically, in maybe their early 40s. At that point, there is usually more than one diopter of residual accommodation. So there's some indication that one diopter of accommodation would not be adequate, or let's say not be ideal for patients to do near work, and that comes from literature other than the IOL literature. So I think that's worth considering.

There is a complicating factor in that as the patients age, their pupil size becomes smaller, and indeed when you do the experiment binocularly, you will get convergence miosis, so you'll end up with an even smaller pupil. So potentially, the argument you make about spectacle independence could be correct. But I would like to have seen some better data on that. I think it's such an important claim for the patient. And I always worry that a claim is made that the patient thinks something different than what you're really claiming. If the patient believes this claim says, oh, I'll be able to see just like I am with my reading glasses, as I am with my

reading glasses, this is probably not going to be true. And I think it would be important to include language that more accurately represents the reality rather than sort of a blanket statement of spectacle independence.

DR. HIGGINBOTHAM: Sponsor, any comments?

DR. PACKER: Mark Packer. I had a slide in my presentation this morning about reasonable expectations for our patients. And in my experience with this lens, and I'll just put this slide up again now so you can take a look at that, I think that the Panel and FDA were right in 2003, that approximately one diopter of accommodation is provided by Crystalens, and now we've seen similar results with Trulign Toric. And as you point out, you know, 1 or 1.5 is kind of what a 40 to 45-year-old, you know, is asking for in addition, right? And that's what we see with these patients.

And to your point, Dr. Owsley, when a Crystalens patient typically has to see some fine print, whether it's the financial pages or the phone book or whatever it is that's smaller than they can see on their tablet or iPhone or smartphone, they'll take a 1.25 or 1.50 off-the-shelf repair reading glasses. That's what they typically do. And so the lens itself, I believe, is correctly labeled as providing approximately one diopter of accommodation.

DR. BRADLEY: Just a follow-up. The question really wasn't about the labeling of the lens. It was more sort of the labeling of the accommodative capability of the lens. It was about the spectacle

independence provided by the lens, and I think the patient needs some clear indications of realistic expectation.

DR. HAYASHIDA: If I may -- this is Jon Hayashida. You know, when we're discussing the spectacle use or spectacle independence data from the study AT45, that was done on bilaterally implanted patients. I know we've stated that before. I think what's an important point of clarification is the first category was asked "I do not wear spectacles," and that was at a rate of 25.8%. The second category was "I wear spectacles almost none of the time," which was really, to the patient, 10 to 25%, and that was 47.7% of the time. So if we would consider that none and some, than that would be, combined, 73.5%.

If we look at -- and, again, it's very difficult to compare against the Trulign Toric, which we've stated in the past that it was on unilaterally implanted subjects. And the questionnaire really wasn't rigorous enough to capture the information at various distances, but at least reporting none and some in total is 89.3%. So, hopefully, that at least provides some level of comparison at least for spectacle use with only a single question being asked.

DR. HIGGINBOTHAM: And this is Eve Higginbotham. So just to just clarify, you did not stratify that by age or by decade in terms of the patient data that you just referenced?

DR. HAYASHIDA: Yeah, it's Jon Hayashida. No, we did not.

DR. HIGGINBOTHAM: Any other questions -- yes, Dr. Brown?

DR. BROWN: Yes, Jeremiah Brown. One of the things we're tasked to comment on is our thoughts about postmarketing surveillance. And, basically, because we have some history with the Crystalens, that's helpful. But the one thing that's going to be very important about this lens is that it be stable in a certain position. So we have good data up to six months. We don't necessarily know one year, two years. Is the lens itself -- like if you pick a 20-diopter Crystalens and a 20-diopter Trulign with 2 diopters of correction for astigmatism, is the weight of the lens exactly the same, or is it a little different, or anything that would make it a little bit different than --

MS. McEACHERN: This is Denise McEachern, Bausch & Lomb. There is absolutely no difference in the dimensions, the material, the design. It's all part of the same thing. So the lens is the same whether it's a spherical 20 power in the toric version or a spherical 20 power in the non-toric version.

DR. BROWN: And the weight also is the same?

MS. McEACHERN: Yes, sir.

DR. BROWN: Okay.

MS. McEACHERN: Yes, sir.

DR. HIGGINBOTHAM: Okay. Dr. Kim?

DR. KIM: Hi, it's Joung Kim. Dr. Packer, in your talk and -- talking about the anterior vault or the asymmetric vaulting, one of the mitigation strategy was the IOL positioning. I just wanted to get a clarification of what you meant with that.

DR. PACKER: Mark Packer. I simply meant that -- to make sure that both haptics are inside the lens capsule.

DR. KIM: Okay. That's what I thought when I caught that from the presentation.

Now, if I understand correctly, in terms of one of the treatment strategies of the vaulting, especially the asymmetric, the vaulting, would be to open the bag and rotate the lens 90 degrees is -- certain things that have been discussed. Obviously, it can't be done with -- that wouldn't be the strategy of choice for a toric lens. Is there any strategies for that, or would that be beyond the scope of what we're looking at here?

DR. PACKER: Mark Packer. No, I don't think that's beyond the scope at all. The preferred treatment strategy at the initial appearance of capsular striae or early in the genesis of a vault would be selective YAG capsulotomy as opposed to a repositioning procedure, particularly with a toric intraocular lens.

DR. HIGGINBOTHAM: Any follow-up, Dr. Kim?

DR. KIM: No, that was it.

DR. HIGGINBOTHAM: Dr. Shen, did you have a question?

DR. SHEN: No.

DR. HIGGINBOTHAM: Any other questions from the Panel?

(No response.)

DR. HIGGINBOTHAM: Okay. Thank you, Sponsor. You can now

leave the table.

Before we bring the FDA back to the table, because I understand there's a follow-up there, and we have to bring the Sponsor back as a result, I would like to suggest that we have a Panel discussion within our own world, if you will, just to see if there are any questions that we may have for each other as we consider the questions from the FDA that we will have to respond to later on this afternoon.

Anyone have any specific topics you'd like to bring up? Dr. -- or Ms. Berney?

MS. BERNEY: My question has to do with patient satisfaction. I'm involved in another study where the vehicle is everything. And how you ask the questions, who asks the questions, which questions you ask are critical to getting to the root of whether people are actually happy or not. Generally, when you ask the questions in a leading way, you get the answer you want to hear. So I'm curious about where the -- how the patient satisfaction part of this actually was conducted and if it was conducted. It's hard to get a good idea of whether somebody is happy if you don't let them tell you how they feel about it as opposed to asking, was this okay, was this okay, or was this okay, because everything could be not okay. You know, can you see 20/20? Yes, I could see 20/20, but I can't see. So there's a "but" attached. So I'm curious about the patient satisfaction portion of this.

DR. HIGGINBOTHAM: Yes. Dr. Bressler?

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DR. BRESSLER: Well, I strongly support the need for that information for all the reasons that you said. In my mind, we're very limited by having validated questionnaires that get at that, even if they were done the exact same way in a randomized fashion to one group and another. So you're pointing out an area where I think we have to improve our research. And, you know, to have yet a new device or something and at the same time have a validated questionnaire that addresses perhaps what that device may help is not always readily available. And that's where I think some of the subjective expertise has to come in in providing advice. So I think your comment should be considered as we're considering the questions. Unfortunately for sponsors or other researchers alike, we're very limited, and you point out, I think, something that's needed.

DR. HIGGINBOTHAM: Dr. Owsley, this is your sweet spot, as they say. Do you want to make a comment?

DR. OWSLEY: Well, just following on from what Dr. Bressler said that that same standard could be applied to the question they did use. And so there's no evidence basis that this question is highly useful either. So if we're going to not have a desired or have patient satisfaction information, I think we have to look very cautiously at the one item they did use or at least the one item they're reporting.

DR. HIGGINBOTHAM: So in your estimation, Dr. Owsley, I mean, how would you judge the functional satisfaction of these patients

based on the limited information that we do have?

DR. OWSLEY: I mean, I just answer that by saying that, you know, that would take considerable thought. But asking people about their spectacle use does not tell you anything at all about whether they're happy with the extent they're using spectacles, and that's really what Barbara was asking about.

Having said that, I do agree with Dr. Bressler, that this is a important measurement area, and when you go to evaluate devices and look at things like quality of life or patient satisfaction, you don't always have a ready-made questionnaire whose psychometric properties are all completely known and you can apply it. It's just -- it would have been nicer to get more feedback from the patients as to the treatment.

DR. HIGGINBOTHAM: Dr. Eydelman and then Dr. Bressler.

DR. EYDELMAN: To answer Ms. Bentley's [sic] question, on slide 68 of FDA's presentations, we're pointed out that neither the parent IOL study nor the Trulign IOL study questionnaire utilized were validated. So both were not validated questionnaires.

DR. HIGGINBOTHAM: Dr. Bressler?

DR. BRESSLER: Neil Bressler. I had no further follow-up except that these comments need to be taken into consideration as we have to make judgments on, you know, safety, effectiveness, risk/benefit ratios.

DR. HIGGINBOTHAM: Dr. Evans?

DR. EVANS: So I just wanted to thank the Sponsor and the FDA for their presentations. I understand the complexities associated with today's proceedings, and I appreciate all of the efforts done to try to understand the data.

I had a number of thoughts as I reviewed the materials and listened to today's presentations. So maybe I could mention the ones that I thought were potentially most important.

I guess the first thing I would mention is I did have some concerns about the quality of the pivotal trial that was conducted. There were clearly a number of protocol deviations, and there's also a lot of discussion about how well the study design and analyses would sort of satisfy some of the draft ANSI documents that are developing.

And then there was unplanned interim analysis, and somebody who -- as somebody who teaches clinical trials, that's usually a pretty major issue. Unplanned interim analyses are usually -- are very much discouraged unless you're really careful about what you're doing. And so because that goes against one of the sort of fundamental tenets of clinical trial operations, I think there's a big question about how much this may or may not have jeopardized scientific integrity of the trial.

And there's two primary concerns. One is sort of statistical in nature, whether there's an inflation for statistical error rates, and the Sponsor and others have done a number of analyses to try to address that.

They did some Bonferroni analyses and things like that to potentially adjust for these multiplicity issues. They did a number of sensitivity analyses dealing with protocol deviations and loss to follow-up, and the results were quite robust to those sensitivity analyses, so I think that was good.

But the second side of conducting -- the second issue with conducting unplanned interim analyses is more not so much about statistical bias but one about operational bias and that if people are reviewing results of that study and have knowledge about those results, that that can influence the way people conduct themselves during the trial. That could happen to a sponsor, to investigators, to patients, and sometimes has a trickle-down effect there. And it can even be -- it can be unintentional; it can be unrecognized.

And that was sort of linked to my earlier question about did you assess whether the masking was successful, and -- because obviously, if results are trickling down and who knows what -- and how much masking was actually done, like, if it was a single mask of the patient. But once you start looking at data, you're sort of open to all sorts of potential biases, and it may or may not be an issue, and we can talk about whether that's the case. But it can certainly affect patient and clinician ratings and their various evaluations. And, again, that could be intentional or unintentional. And fancy statistical methods, unfortunately, can't rescue that problem. And as I was reading, you know, some of these measures certainly have the potential to be

affected by a placebo effect or an effect of belief as well.

So that was sort of one issue. I think perhaps another issue that may not be a huge issue but I think could warrant a bit more discussion, and that's sort of the evaluation of the reasons for dropout and loss to follow-up, because much of the analyses that are presented are basically based on data that are observed at Form 3 or 4 and so on. And what we have to convince ourselves is that if that's what we're analyzing, that what we're analyzing is representative of what's really going on.

And you've got a randomized clinical trial, which sort of guarantees you expectation of balance with respect to everything else whether you know about it or not, whether you've measured it or not, but as soon as you start discarding patients, a randomized clinical trial becomes an observational study, and you don't have that expectation behind you anymore. And so you have to be really careful about how you interpret that unless you can convince yourself, again, that the reason for the loss is not informative, that it's somehow random. So I think that's something to consider.

There was also one point made where there was a sort of secondary or follow-up analyses that did an adjustment for MRSE, and I was just curious about where that model came from, whether that was sort of pre-specified or whether there was a precedent somewhere, because the sort of standard unadjusted approach, which under a randomized clinical trial

should be valid, was clearly not significant, but after the adjustment, was, and I think the one thing I want to be careful of is that there wasn't many, many models fit and then all of the sudden we pick the one that's most favorable, and somehow the one with the lowest p-value becomes the one reported. And I'm not saying that's the case. I just want to know the rationale for the model and where that came from.

I think that, I guess, the last issue I had, there was a lot of talk about gender effects and age effects. And I think if you take a close look at what was happening, I'm less worried about the gender effects. Certainly a very important issue, but certainly, there were sort of effects in the same direction in positive for both males and females, so I think that may be less of an issue.

But the age thing is a little bit different. It's sort of trending in the -- you know, this is supposed to be a superiority trial, and there was a trend that, at lower ages, it was no longer superior. And so I think that warrants sort of critical evaluation and a careful look. Now, granted, the numbers are small, and there are a number of issues.

And the other thing to note about that is that it wasn't necessarily the issue that the investigational device became less effective. It was that the control arm became more effective in some sense or loses its effectiveness with higher ages. That's sort of what appeared to be happening, and that may warrant some discussion, and there may be some

prior data behind that.

Thank you.

DR. HIGGINBOTHAM: Dr. Evans raises a number of key questions here. First, related to the conduct of the clinical trial and the unplanned analyses that were done subsequent to at least some of the initial collection of data, and then finally, the gender -- the age question related to the data.

Dr. Bressler, do you have any comments about the interim analysis as perhaps one specific first question?

DR. BRESSLER: Just to emphasize what Dr. Evans said, so you may ask, well, does it really matter if you did these unplanned analyses and you adjust for them afterwards to look? And it really does matter when you are asking is something safe, for example. You're sampling people, and you're saying how confident are we that the data in our trial is representative of what's going to happen when this is in the real world.

And so if you take a look -- and let's say they happen to have had a problem with the people they had, and let's say there really is a problem that wasn't identified in this group. If they had not identified that in this small group that they did their interim analysis and they go on, but the true answer is that there was a problem, you bias going forward with the study. Now, and you may say, oh, but we enrolled everybody and we, you know, we were still doing the analysis, but it introduces a bias that you

cannot be as confident that your safety is reflective of what you're trying to say.

So that's why you try to avoid it at all costs, because it just weakens your confidence in the group that you're looking at. You might not have gone on if you saw a big problem in it, and it wouldn't be presented today. So you're cherry-picking in a way the studies that then get presented. Now, I'm sort of taking it to an extreme example, but just saying why I think it's important. So if you have no other biases, then that's not a problem. Then when you have protocol deviations, you have not an intent-to-treat analysis, these can add to the loss of confidence in the data. So I only wanted to echo, I think, what Dr. Evans said.

I didn't agree with the age thing. I think the number is too small with that small group that I can't say one way or the other that there's something there, and so if they took people who were 62 to 64 and found out -- I know that's not what you said -- that something funny happened with that group, I wouldn't know what to make of that either. So the age thing, to me, is inconsequential at this moment because it's such a small number.

DR. HIGGINBOTHAM: Any follow-up, Dr. Evans?

DR. EVANS: No. I appreciate those comments. I guess my only follow-up on the age comment would be that, you know, I guess I would agree that I wouldn't necessarily say that we've shown that for lower ages, that this is not superior or not effective, but that's where the burden of proof

is. And so that's why I make that statement.

DR. HIGGINBOTHAM: Okay. Any other questions? Any other cataract surgeons who would like to comment on the concern about vaulting? Does that bother you in terms of the risk of vaulting of these lenses? Dr. Kim?

DR. KIM: I think I would comment on it in terms of handling it. And if it's going to be any more -- you wouldn't expect this to be any more likely to occur with this one than, you know, than the parent IOL, but just in terms of handling it, if it is changing -- the position of it, obviously, that's going to be different with a toric lens than a non-toric lens.

And I guess one other comment when they come back up, too, would be whether with a toric lens and it vaults, was the induced astigmatism giving much higher than just the standard tilt induced astigmatism that you get in a non-toric IOL.

DR. HIGGINBOTHAM: Dr. Shen, do you want to comment on the technique or the complications related to -- potential complications related to this lens?

DR. SHEN: You know, having had some clinical experience with the lens, I mean, it is, you know, it's difficult because there's 20% of the patients who are not going to get an accommodative effect, and how do you counsel them with the labeling that there is? And then, you know, discussing you're going to need possibly treatment for Z-syndrome. I mean, I think it

just is involved in the discussion with the patient that's got to come from the provider who is going to put the lens in.

DR. HIGGINBOTHAM: Dr. Steinemann, did you have a comment?

DR. STEINEMANN: I agree entirely. It's patient selection and counseling and proper expectations and setting the stage of those expectations that's absolutely critical in this whole process.

DR. HIGGINBOTHAM: Dr. Harris?

DR. HARRIS: David Harris. In exchanging or moving a Crystalens -- obviously, I've never put a toric one in so -- or had to spin one because its axis was wrong, but I've had to remove them or exchange them because of spherical errors and so forth, and they are a little bit more technically challenging, I believe, to extract out of a capsular bag and leave the capsular in such a state that a new lens could be put in at the exact angle or axis that you want.

Say, compared with extracting a lens -- a three-piece lens with polypropylene or other haptics or a one-piece acrylic lens, both of which have their challenges, the one question I would have, though, if this is a lens which is occasionally going to require replacement or repositioning especially in terms of its angle, the type of -- because of the criticality of having the feet in -- the haptics right into the capsular equator, I would think that, you know, if I was going to try to turn one of these 20 degrees, for example, I don't know

how sure I'd be that if -- even if I could separate the leaflets atraumatically and move it over there, whether I was now -- is it going to be more bunched, more likely to vault, more likely to tilt?

So these are just some questions I have which we can't answer here. And I don't know if any of the representatives from Bausch & Lomb have, you know, maybe had more experience swapping or moving these lenses might have a comment. But that's an issue that, you know, that any problems -- we have to look at whether -- I feel as a Panel, any problems that we look at in terms of the safety side, we have to look at the safety of repairing them, too, and in my field, as I'm sure with many other Panelists here, we've had unhappy patients with both accommodating and multifocal or other lenses that are required. My experience is it's a little harder to manipulate these lenses than it is some of the other styles.

DR. HIGGINBOTHAM: Is your level of comfort inserting this lens the same or any different for a +1.25 diopter astigmatism eye versus one that has higher astigmatism?

DR. HARRIS: Again, having not, you know, placed a toric one, I don't think so, no. The placement doesn't bother -- that's not an issue for me. It's the idea of if you had to swap it or move it.

DR. HIGGINBOTHAM: But in terms of the potential benefit of the patient, is there a difference in your mind as a cataract surgeon in offering it to a +1.25 diopter astigmatism eye versus one that's higher?

DR. HARRIS: I'm not sure I understand your question, Eve. I'm not sure I understand what the -- maybe --

DR. HIGGINBOTHAM: Dr. Shen, I saw you shaking your head.

DR. SHEN: Yeah. I think she's asking, you know, if it's the, you know, the low versus the medium versus the high amount of cylinder correction, would you feel that it would be just as easy to correct the high level astigmatism as opposed to the 1.25?

DR. HARRIS: I think it would. The low versus high is not an issue for me. It's just that when you -- the higher ones, you're going to be more sensitive to the -- how correct your axis is, and so therefore, perceivably, you might have -- you know, the patient with a 10-degree off axis and the larger one is going to be more unhappy or have a bigger issue than the one in the smaller one, and so you might be more likely to have to go back and spin it or do something like that. But the actual implantation I don't think is an issue or even getting it at the right axis.

And the study physicians, you know, probably have -- presumably were all experienced in placing Crystalenses in the first place, and it's not -- wasn't a huge leap for them to -- all they had to do now was just to -- you know, maybe in the past, they all were placing their incision in the steep axis, which may or may not be awkward compared to their norm, but the only difference with this lens is that they, again, got to make sure it's at the right axis.

But, again, I don't think the placement of it would be -- of the high versus the low would be an issue.

DR. HIGGINBOTHAM: Yeah, I suppose it's not so much the placement, but the risk/benefit considerations when you talk to the patient related to low, moderate, or high astigmatic error.

DR. HARRIS: Frequently, patients that have -- they don't -- other than the unusual patients who has some sort of lenticular cylinder which is counterbalancing corneal cylinder, generally, in terms of counseling patients, the patients with the higher cylinders are also the people who sort of have more to gain from this thing. They're the ones that are going to be happier if you get it right. And I think they've -- from what I've seen from the discussions here, that it's not hard to get this lens in the axis that you intend to put it in.

DR. HIGGINBOTHAM: Any other comments or -- Dr. Feldman, I saw your hand.

DR. FELDMAN: I think that, clearly, being able to correct 1.25 in each, the low, medium, high, is going to -- would offer benefit to the patients, and it's hard to assess, you know, which patients would benefit more from that, as each patient is affected by their astigmatism differently. Some patients are more comfortable with glasses, and some really value spectacle independence more.

Kind of circling back a little bit. So the vaulting. One thing that

I was assured by was the low rate of the vaulting, but one thing that concerned me when looking at the safety outcomes of the two patients who did have the vault, neither one of them really had a course after that was taken care of. And, in fact, one of the patients was lost to follow-up, and the other patient had persistent corneal edema. So that's a little bit concerning and kind of goes to what Dr. Harris was talking about in terms of the difficulty sometimes in managing these lenses if they do go on to vault or if they have to be exchanged. And that's particularly worrisome a little bit in this situation because these are investigators who are well-versed in the use of this lens and some of the techniques to decrease the incidence of the vaulting. So that's something to consider.

DR. HIGGINBOTHAM: Thank you. Any other comments that --  
Dr. Coleman?

DR. COLEMAN: Yes. This is Dr. Coleman. And I have a question for my fellow Panel members. On slide 82 that was presented by the FDA, for the original Crystalens study for the accommodative amplitude, it was about 90.1% got that distance corrected near visual acuity of 20/40 or better. And I'm having a hard time figuring out why it was only 64.6% of the control subjects in the Trulign study that got this. Maybe it's because they have astigmatism that was more than that in the Crystalens original study. But then why when you're correcting the astigmatism in the Trulign subjects it's just 62.9%? Does that mean that there's something about the astigmatism

on the posterior surface that's affecting it? The accommodative amplitude is not where I would expect it to be. And so it's bothering me.

DR. HIGGINBOTHAM: Would any Panel members like to -- otherwise we can save that for Sponsor and FDA as a question.

Any other questions? Dr. Clayton, are you satisfied with the gender question?

DR. CLAYTON: I still -- well, I appreciated the slides that the FDA showed, and I'm assured that things don't look different between male and female. I still have some lingering questions about what might be the situation for younger women in the 60- to 70-year range, but their numbers are very, very small, and -- but one of the questions that we're asked to respond to is this age issue. So I do still have questions about that.

DR. HIGGINBOTHAM: Okay. Well, I believe we can invite the FDA -- yes, Dr. Harris?

DR. HARRIS: Dr. David Harris. I'll make one more comment relating to Dr. Coleman's question. In my practice again, I -- and maybe -- cornea doctors as opposed to mainly cataract doctors will attest, patients come to us when they're having problems with intraocular lenses just like with Dr. -- Ms. Berney, the patients she's seeing are the ones who are having trouble. There may be 99 happy ones for every one trouble -- same with me in intraocular lens patients. But when I've had patients in the earlier phase of the Crystalens come see me, my experience is that no way that 90% of them

see -- you know, have good uncorrected near acuity. I think there's something wrong with the early data, and this data is probably the right -- the 60% is more realistic.

DR. HIGGINBOTHAM: All right. Before we invite FDA back, I'm going to turn to Dr. Tarantino to see if you have any other questions or comments you'd like to have the Panel discuss.

DR. TARANTINO: Yes. This is Nick Tarantino. There is a couple things that I was looking at relative to the age data. And when you look at the scatter plot, it looks like there was a couple patients -- and because the sample size was relatively small in some of the ages, it looks like there was a couple patients that really contributed to the data that we see. So I'm just wondering if anybody had noticed that, too. It was slide --

DR. HIGGINBOTHAM: Slide 92 in the FDA packet?

DR. TARANTINO: Yeah, slide 92. Can we see that one? Is that possible? Oh, I guess we all have it in front of us. So, you know, if we look at some of the younger patients, again, there's very few of those, but there's at least one that I think, you know, does something on that. And then when we look at the older patients, there are a few that I think affect that significantly, too. And I'm just wondering because of the small sample sizes, maybe this might be a little spurious in terms of what we're seeing.

DR. HIGGINBOTHAM: Yes. Okay. Yes, Dr. Eydelman?

DR. EYDELMAN: We're bringing that slide for you.

DR. BRESSLER: I would just say, again, that --

DR. HIGGINBOTHAM: Dr. Bressler, thank you.

DR. BRESSLER: Neil Bressler, sorry. The numbers are tiny, so if you look at the people who are, you know, between 70 and 80, there are people who are way down there, with very little reduction in cylinder. If they just happened to get one of those people who are in their 50s, but they only had about, you know, seven people looked at, it brings the average way down. If on the other hand, if you did 100 people and they were all down there, then you would say, okay, now we have something. To me, when you just divide it like that, it's not there.

So then I ask, okay, are there other data to support that? We don't have any other data that I know of in the literature to support why there should be a difference. I haven't been given a biologic rationale when people are asked. So, again, I'm leaning more towards when you divide things out and you have small numbers, that's going to happen sometimes, and it doesn't concern me because of the absence of other information to go with that or any strong biologic rationale.

DR. HIGGINBOTHAM: Okay. Thank you. Dr. Leguire, do you have any comments or questions for the Panel?

DR. LEGUIRE: Well, actually, I wanted -- regarding this graph here, I'm sitting here silently but thinking, well, if you drop those under 60, you're still going to have an age effect interaction. If you drop those --

maybe all of those at the 75 to 80, you may lose the effect. I'm not sure. But at some point, you have -- you know, all of these data contribute to the many regressions, and all of the data contribute to interaction effect. And so we see people want to drop these or discard those under 60, discard those under 80. At some point, you have an effect. And for my eyes, there's clearly an interaction effect here that will not dissipate if you throw all those under 60 away, and there's a big clump, I mean, God, 2, 4, 6, 8, 10, 12, 13 patients between 75 and 80 that are just clumped down there. And, you know, they're a separate distribution from the others. And so from my statistical mind, there really is an interaction effect here, and you have to explain it.

DR. HIGGINBOTHAM: Dr. Evans, would you like to comment on this point?

DR. EVANS: Yeah. I think the data support that there's likely an interaction. I'm sure that there are some overly influential points on this plot, and there are some ways to get around that. You can do regression on ranks and do something non-parametric where it sort of dampens the effect of any one or two particular outliers. But I tend to agree that although that would dampen the effect of, you know, some of the extreme values we're looking at, I think there's probably still some interaction here. And, you know, I see -- you know, I tend to see a little bit of a trend. I guess the part that sort of stands out to be a bit more here is not necessarily that there is a whole lot of change with respect to the outcome as age -- the change that I'm

seeing is actually in the control arm, that, you know, the control arm is relatively effective at younger ages, but when they get older, it drops off. And, therefore, that's where you see -- start to see the signals. That's sort of what I see.

But, you know, there are other sort of analyses that could be done that'll just dampen the effect of sort of extreme observations. But I think you'll still see a little bit of an interaction here.

DR. HIGGINBOTHAM: Okay. Yes, Dr. Bradley?

DR. BRADLEY: Just a follow-up on that. We have to remember this is a plot of percentage, and a small error of a small intent could be a very large percentage of that, of the target. So it would be much more informative to see this data plot in real diopters as opposed to percentage.

DR. HIGGINBOTHAM: So we will invite -- if there are no other questions or comments at this time, then we will invite FDA back to do some follow-up comments, and then subsequently, we'll ask the Sponsor to come back to the table. So any questions that you have actually created in your own minds as a result of this discussion, this is your opportunity to ask them first to the FDA, then to the Sponsor.

Dr. Leguire?

DR. LEGUIRE: Larry Leguire. You know, the elephant in the room, I feel, is accommodation, and does the lens really accommodate or not. And I think of false advertising if you say it's an accommodative lens, but

there's no data. And I -- you know, I want to bang on the FDA panel 10 years ago that went ahead without data saying that this is an accommodative lens, but here we are, 10 years later or whatever, and I'm still not convinced, given the data, if it's an accommodative lens or not. Clearly, the Sponsor has shown conversion lines of evidence that there may be some "accommodation" or at least change in the dynamics of the lens. But then the FDA people get up and go on, well, you know, the literature is very ambiguous at best, and at worst, it shows that the lens does the opposite of what it's intended to be.

From my perhaps simple approach before I even I read this and I saw accommodating IOL, I said, oh, great, you know, I got a cataract and maybe in 20 years I'll have it fixed, and this is a great lens, it accommodates, I'll be able to see closer better. But lo and behold, wait a minute. You know, you can't see any closer, any better closer, so I'm -- it's this whole accommodation thing that really has me going here.

And so maybe we can discuss within ourselves first, you know, what is our opinion about whether this lens really accommodates, and if we can't -- if there's no clear evidence that it accommodates, then how can we call this an accommodating IOL even though the parent has that designation?

DR. HIGGINBOTHAM: Is that a question you're posing to your Panel colleagues?

DR. LEGUIRE: Yes.

DR. HIGGINBOTHAM: So I think FDA will have to leave the table while we continue our deliberations.

DR. EYDELMAN: Can we just stay hooked up?

DR. HIGGINBOTHAM: All right. Okay. Thank you.

Okay. So anyone would like to respond to Dr. Leguire's concern? Dr. Leguire is our Consumer Rep today, is it?

DR. LEGUIRE: Yes.

DR. HIGGINBOTHAM: Yes. Did I get that right? So just wanted to state that for the record.

Dr. Bradley?

DR. BRADLEY: I think the point raised is a good one, and I think you're right, in some ways, it's the elephant in the room, and unfortunately, this particular dataset that we're looking for was not collected on the lens we're examining today, and I think that's rather unfortunate. But that's the reality we find ourselves in.

A couple of comments. First off, a patient who gets an IOL -- and they don't get it because it's accommodating or it's multifocal or pseudoaccommodation. They would get that lens and be happy with it if they have functional near vision. This is what they're targeting. So I think from an issue of function, whether it's accommodation or not accommodation, it sort of preps an aside for the patient --

DR. LEGUIRE: (Off microphone.) Not an educator.

DR. BRADLEY: But I do think in terms of labeling, it's a very critical issue. The question is does this lens truly accommodate, or are we seeing some other factors that are providing enhanced near vision. Typically, they've been all pitched into one sort of category, and unfortunately, it's called pseudoaccommodation, which is probably not a very good title. So do we have genuine accommodation, which is an actual change in the refractive power of the eye, or do we have a pseudoaccommodation, which are multiple factors, you know, change in pupil size, spherical aberration, even astigmatism can help.

Another interesting one, of course, as I asked earlier about the mean spherical equivalent that was determined, these patients are all slightly myopic. This is, again, another way to enhance near vision without accommodation. There are multiple ways that can happen. And I think the FDA has challenged us today to try to come to some decision on whether we believe this lens is truly accommodating or whether it's providing near vision through some other mechanism. And I would characterize that as is it an accommodating IOL, is a pseudoaccommodating IOL, or is it both? And my suspicion is it could be both. It could have features of this lens that enhance the depth of focus and therefore enhance what's called pseudoaccommodation. But it also can have features which allow it to accommodate.

So I think, in that sense, we have to decide, are we talking

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about a labeling issue or are we talking about a patient satisfaction near vision function issue here? And my personal feeling is, yeah, I like the labeling to be correct. I like the patient to know what they're getting into. So I would like us to examine that carefully.

DR. HIGGINBOTHAM: Ms. Berney, do you want to comment on this issue?

MS. BERNEY: Well, I was reluctant to bring up the elephant in the room because I'm just an artist. But when I look at the -- I don't have the slide in front of me -- when I look at the spread and I see how few of those people have near vision and how many are 20/40, it makes me wonder just how effective that is. And as a patient who has been fed a line and swallowed it, believing everything I was told, I'm naturally very cautious. So if I were to read something that told me this or my physician said, "Oh, you'll be able to see at all distances," I personally would find it hard to believe that. I would like to see something that definitively shows that this truly is accommodating. And I am not seeing that.

DR. HIGGINBOTHAM: Okay. Dr. Bressler?

DR. BRESSLER: There may be specific definitions that the FDA uses for the term accommodation. And I think to the layperson, it probably means being able to see at various distances. And if that's what the acceptance is, then there's evidence that's been shown that it's effective at seeing at various distances. Whether it's very effective or somewhat

effective is a different story, but if the definition is what ophthalmologists think of, which is accommodation due to relaxation or contraction of the ciliary muscles, then we don't have evidence of that that we've been presented at least.

And so to me, that's where it comes down to. And I think people often do interpret if they see accommodation, as an ophthalmologist, that you're talking about something that is dependent upon the relaxation or contraction of the ciliary muscles, this is why, which is a little different from just the broader layperson of it accommodates at different distances. I like labels to apply to the physician so the physician can then have the interaction with the patient to educate. Yes, many patients will read these labels as well, and that's fine for continuing the discussion.

DR. HIGGINBOTHAM: Ms. Berney?

MS. BERNEY: I think that that reinforces what I feel about the patient labeling especially. I know that, because I work with lots of surgeons and eye care providers, I know that the information they get is different than what the patients get, and I know that if you are unaware of what those terms mean, you can get a surprise, because you are not familiar with that terminology. So I think we have to be very careful about what is presented to the patient as well as what's presented to the physician.

DR. HIGGINBOTHAM: Okay. Great. Seeing no other hands raised or body language indicating that you're about to raise your hand, I

would like to invite FDA back to the table for follow-up questions and comments, and their presence will be followed by that of the Sponsor's, and we'll do the same.

DR. HILMANTEL: I'm Gene Hilmantel. There's a couple of things that we'd like to try to answer that were prior questions. I believe it was Dr. Feldman who had asked if we had asked for whether the surgically induced astigmatism was affected by age, whether we had asked for that analysis. Unfortunately, I didn't remember, but we had. We asked for about 100 different analyses.

So the Sponsor did provide that analysis, and there was no significant age effect and no interaction. And that slide that just disappeared shows the surgically induced astigmatism by age.

DR. HIGGINBOTHAM: Do you have the -- this is Dr. Higginbotham -- the legend? I don't see -- what's the red line that --

DR. HILMANTEL: The red line, I believe that was some sort of higher order FID. It was --

DR. HIGGINBOTHAM: The green line, the dotted line?

DR. HILMANTEL: Yeah, well, the green line was a linear regression FID and the dots are the actual data points, and the red line looks like it was a, I don't know, fifth order term FID or something like that, the red line. And the dotted lines were confidence intervals.

DR. HIGGINBOTHAM: Is that clear to all Panel members

because it wasn't clear to me. Okay. Dr. Clayton?

DR. CLAYTON: I agree that it wasn't clear without the legend, but --

UNIDENTIFIED SPEAKER: (Off microphone.) Do we have a legend?

DR. HILMANTEL: No.

DR. HIGGINBOTHAM: Any other comments from FDA, follow-up? Yes?

DR. KIANG: Yes, we also have -- it was asked about whether we had additional information about age effects, and we have an additional regression.

DR. HIGGINBOTHAM: You should plug in that other computer, too, by the way.

DR. LU: Laura Lu, FDA statistician. I would like to provide a little bit further discussion on the treatment group by age interaction. We have heard several Panel members have concern about the whether the interaction is driven by the lower age group, less than 60. We mentioned the age group less than 60 because the group categorization was done in one report by the applicant when reporting patient demographics and also when the applicant did the treatment by age analysis. But, actually, we have the exact age, so we don't need to artificially or randomly categorize patients here.

Here, I want to explain that actually there's -- the trend that the treatment effect is diminishing as the patient age gets younger is not driven by the patient group less than 60 years old. This slide, our backup slide, shows that even when we exclude those patients less than 60, which is seven patients in the toric group and 11 patients in the control group, there's still a pretty clear treatment by age interaction, and the p-value is .005. And you could see that the separation is -- in trend is pretty strong. Without those patients less than 60, you can still see that the two lines are about to cross at age 60.

DR. HIGGINBOTHAM: Yes, Dr. Harris and then Dr. Bressler?

DR. HARRIS: I don't understand this graph at all because it says percent reduction in absolute cylinder -- it looks like some of the points have more than 100% reduction in absolute cylinder, but you can't have negative -- you can't have a negative effect. So, like, what is -- when it's 130% reduction of absolute cylinder, what is that?

DR. LU: Okay. Dr. Hilmantel?

DR. HILMANTEL: So Dr. Mokhtarzadeh -- my name is Gene Hilmantel. Dr. Mokhtarzadeh does have a slide explaining that the percent reduction is the percent compared to the intended reduction. So some patients do achieve more than the intended reduction probably due to the surgically induced astigmatism being greater than expected.

DR. HARRIS: So you mean, like, someone had 3 diopters of

astigmatism to start out and you were intending to knock off two of them, and so you're not making these people have some other kind of cylinder -- okay, I understand. So these people with more than 100% reduction are people in which you're not intending to correct all of their cylinder, I guess?

DR. HILMANTEL: Yeah, that's absolutely correct. So in your example, if you start out with 3 diopters of astigmatism, you're intending to correct 2 diopters, if you end up with 0, so then you've achieved 150%.

DR. HARRIS: Thanks. I appreciate that clarification.

DR. HIGGINBOTHAM: Dr. Bessler, you had an earlier comment?

DR. BRESSLER: If you'd put that up again, I just want to emphasize that the p-value says you're very confident that there is some interaction there. It doesn't tell you that the interaction is big or small. It just says I'm very confident of what the interaction is. The interaction is just, again, unusual or challenging for me to be concerned about because I see that over -- first of all, there's a big scatter there, you know? There's not a lot of points and they're sort of spread all over the place, and yes, they tend in the control group to change over time; they don't seem to do that for the treatment group. So, again, I'm just saying from a clinical aspect, I can't put a lot of concern, let's say, because the questions that we were posed is, is there concern about something over age in this toric group, and so I'm just giving you my impression.

DR. HIGGINBOTHAM: Does it at least raise a question in your mind that there may be an interaction based on the data that's been presented?

DR. BRESSLER: Neil Bressler again. I don't have a good idea of why that control group should change over time, so again, you know, if you tell me that that was found in other studies of, you know, these lenses in the absence of the toric, then, you know, I might say that.

DR. HIGGINBOTHAM: Dr. Feldman, you had a question?

DR. FELDMAN: Yes. Speaking to that same question, I'm curious if 10 years ago when this was initially presented, if we saw differences in astigmatism or if that was measured along patients who had the parent lens and if that changed with age? I know these patients had less astigmatism, but was that something that was looked at, and was there an age effect with that study? Perhaps we don't have the answer?

DR. EYDELMAN: I think we would have to get back to you on that because the approval was more than 10 years ago.

DR. HIGGINBOTHAM: Does that suggest, Dr. Eydelman, that's going to be today?

DR. EYDELMAN: If you wish, we can try, or we can table that.

DR. HIGGINBOTHAM: Okay.

DR. FELDMAN: And just following up on that, I'm also not concerned by it since it's in the control group and that toric line is almost

completely flat. It's pretty convincing to me that there's not much of an age effect to what we're assessing here today.

DR. HIGGINBOTHAM: Any other questions for the FDA? Yes?

DR. KIANG: We also wanted to address the question regarding our slide 82 regarding the distance corrected near visual acuity and the difference between the control group that was -- in this study versus the Crystalens study, the 64.6% versus the 90.1%.

DR. HILMANTEL: Gene Hilmantel. I don't really have an answer to the question, but there has been speculation that at least part of the effect of the Crystalens is due to aberrations in the lens that provide some degree of multifocality. So the original Crystalens study was on the 4.5 mm lens, and that is coming up. So the original Crystalens was on the 4.5 mm lens, and so that being a smaller diameter, that would have more spherical aberration and could conceivably give more -- a greater degree of multifocality, giving better near vision, if that's a significant factor. This study on the Trulign Toric was on the 5 mm lens, so that would have somewhat less spherical aberration. So that's not really an answer, we don't have data, but that's a possible effect. In addition, the 5 mm lens has slightly shorter lever arms for the haptic to push the lens forward because the optic is larger, but the calculations indicate that that would be a very minor factor.

DR. HIGGINBOTHAM: Dr. Coleman, did you have a follow-up? I think that was your question. Dr. Bradley?

DR. BRADLEY: Yeah, this is a follow-up question. It was my understanding that there was a design change when we went from the original Crystalens to the Crystalens HD. And the study today with the Trulign is using the Crystalens HD platform? No? The original? The original, okay. Thanks.

DR. HIGGINBOTHAM: There was a head nod in the affirmative from the FDA.

DR. EYDELMAN: And there is a slide being projected.

DR. KIANG: This shows the design -- this slide shows the design changes and how they relate to the current lens under question. So you can see that you have the original Crystalens, which was approved in the original PMA. Then we have a design modification for the 5 mm optic, and the toric lens is a modification of that. The HD is another modification that had a 5 mm optic and also an aspheric button.

DR. HIGGINBOTHAM: Any other questions for the FDA?

(No response.)

DR. HIGGINBOTHAM: Any additional comments from the FDA?

DR. KIANG: We also have a comment regarding the question of the data from one site again.

DR. LU: We actually exclude the largest investigator site, and the treatment effect in that -- recall that the overall treatment effect is about 35% advantage for the toric over placebo -- actually, in that one center, the

treatment effect is lower than the average. So when we exclude that treatment center, the overall treatment effect by combining other centers becomes 43%, which is larger than the original one, and the p-value is still less than .001.

DR. BRESSLER: Neil Bressler. Thank you. And just to clarify, you're talking about just the 1.25 versus the control, right? You're not including the other uncontrolled --

DR. LU: Right, right.

DR. BRESSLER: Thank you.

DR. HIGGINBOTHAM: And could you state your name?

DR. LU: Laura Lu.

DR. HIGGINBOTHAM: Thank you. Any -- oh, Dr. Feldman?

DR. FELDMAN: Yeah. Just one quick point here I wanted to ask about. You had mentioned some design changes that may account for the reason that we see the near vision change 90% to down to the 60% with this 5 mm optic versus the 4.5 mm optic of the original Crystalens that was approved 10 years ago. Since the July 2007 -- in the July 2007 approval of the more similar Crystalens, the 5.0, do we have data as to the near vision percentage in that group, which would be more similar to -- as a parent lens to what we're evaluating today?

DR. HILMANTEL: Well, that Supplement 14 on the Crystalens HD, that was a completely different design. That has --

DR. KIANG: (Off microphone.) He's talking about the five-o.  
He's talking about the --

DR. HILMANTEL: But he mentioned the HD -- let me just -- and so the HD study that had a near add, a small, like, a one diopter add to -- in the center, so we did not have clinical data on the 5.0 conventional spherical design.

DR. HIGGINBOTHAM: Gene, can you state your name, please?

DR. HILMANTEL: Gene Hilmantel.

DR. HIGGINBOTHAM: Dr. Bradley?

DR. BRADLEY: Just a follow-up on the question that we just heard. The Sponsor presented a slide CL-4 in which they showed a through-focus plot of visual acuity as a function of target distance for eyes where they had zero astigmatism, looks up to 2 diopters of astigmatism, and indeed, the ones with the more astigmatism, which presumably in this case would be eyes that were not corrected, although they have inferior distance vision, they have slightly superior near vision. So that could be the reason for this difference that we're observing.

DR. HIGGINBOTHAM: Dr. Bradley, could you help us locate the slide that you're referencing?

DR. BRADLEY: It's on page P-8, bottom slide, CL-4. And it might be appropriate at some point for the Sponsor.

DR. HIGGINBOTHAM: Okay. Any other questions for the FDA,

and any comments from the FDA either on this last question or any other questions that have been raised?

DR. HILMANTEL: Gene Hilmantel. There was a question earlier about the definition of an accommodating lens, so the draft ANSI standard on accommodating lenses does have a definition in the standard. So I'll just read that if you don't mind. It's "a lens that's designed to provide vision over a continuous range of distances by effecting a change in the vergence power of the eye" -- I need an accommodating lens here.

(Laughter.)

DR. HILMANTEL: What's that word?

DR. KIANG: Resulting.

DR. HILMANTEL: -- "of the eye resulting from the implant." So that's it.

DR. HIGGINBOTHAM: Thank you for that clarification. All right. Thank you, FDA, for your --

DR. EYDELMAN: I think we're done.

DR. HIGGINBOTHAM: -- work and due diligence on all of our questions.

I'd like to invite the Sponsor to return to the table once the FDA has left the table. The FDA has now left the table, and Sponsor has now returned to the table.

As they're assembling, Dr. Bradley, would you like to restate

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your last question?

DR. BRADLEY: Yeah, this is Dr. Bradley. On page 8 of your presentation, there's a graph which may pertain to the questions that we were having about the differences in the quality of near vision provided by the Trulign versus the original non-toric version of the Crystalens. And in my reading of this graph, which I think was what was in the presentation this morning was that, yes, when you have the toric correction, you have a dramatic improvement in distance vision, but you do have a small loss of near vision. And is that potentially the explanation that we're seeing for the differences in the -- or the reduced quality of near vision provided by the current lens design versus the earlier design?

DR. PEPOSE: Jay Pepose, medical monitor. Well, that would pertain only to eyes that had against-the-rule astigmatism. With with-the-rule astigmatism, you would have degradation at all vergences.

DR. BRADLEY: Yeah, I guess I don't understand that answer. Sorry.

DR. PACKER: This is Mark Packer. This graph is from a publication unrelated to this study, but I think useful nonetheless because what they did, what the authors did here was to sequentially add .50 diopters steps of against-the-rule astigmatism to measure the effect, measure the blur at different vergences. So the addition of astigmatism creates a very significant blur at distance, at infinity, as you see on the far right. At 1 meter,

although that blur is still statistically significant, the differences are much tighter. And actually at near, the residual against-the-rule astigmatism has a somewhat salutary effect on vision.

So what we would expect to see in those subjects who have residual against-the-rule astigmatism in the control arm of our study is somewhat better near visual acuity. For those with residual with-the-rule astigmatism, steep at 90 degrees, we would expect to see somewhat degraded visual acuity at all vergences. And these same general principles would hold but to a lesser degree in the treatment group, which had much less residual astigmatism.

As to whether or not this could help explain the difference in uncorrected near vision that we see in this study versus the original AT45 PMA, I think it's possible. However, I think there may be many factors that go to explain that difference. And I think trying to explain it would be fruitless speculation, in all honesty.

DR. HIGGINBOTHAM: Yes, Dr. Bradley?

DR. BRADLEY: Just a follow-up. Yeah. I think the implication of both answers is that somehow one particular type of astigmatism is more detrimental to visual acuity than another type of astigmatism. And I think, notably, I think studies show it's oblique astigmatism that is the most detrimental, and whether you're blurring the horizontal or vertical is not -- doesn't produce a large difference in the visual impact. So with or against-

the-rule astigmatism I don't think is such an important factor here.

DR. HIGGINBOTHAM: Dr. Harris?

DR. HARRIS: I have a question about the algorithm in the toric calculator used for this study. One of the slides indicates that, for example, for the 1.25, that it would have an approximate corneal effectiveness of about .83 diopters of astigmatism. And that says the range of expected -- so that the 1.25 lens would be chosen for a patient whose expected postoperative cylinder would be between .83 and some other number -- I don't have the slide in front of me. Does your algorithm assign -- I know how it assigns the axis, but in terms of the power it's assigning, is it shooting for an average?

In other words, is it going to recommend the 1.25 exactly for people whose exact postoperative keratometric cylinder is supposed to be .83 and that number, or is it shooting for -- and is that -- if you're doing that, I'm assuming it's already also calculated in the presumed .5 surgically induced astigmatism and all that turned out later to be .7 -- it's calculating that in. Is it shooting for the low end in order to avoid overcorrections, or is it shooting for the middle of what you're looking for? In other words, is it going to pick a lens which is going to correct as much astigmatism you have up to a certain point, or is it going to -- trying to shoot for the middle, if that makes any sense?

DR. PACKER: Mark Packer. Yes, that makes complete sense.

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It's targeting a slight undercorrection. So that lower limit is put there so that we don't end up with overcorrections.

DR. HARRIS: I just was -- had to do with my earlier question about the graph, how you could have 130% -- I understand if you're shooting for a little undercorrection, then okay. Thank you.

DR. HIGGINBOTHAM: All right. Any other questions for the Sponsor? Yes, Dr. Feldman?

DR. FELDMAN: Acknowledging the success that you had in the approval of the 45 and noting that there's been an evolution in the Crystalens, can you just give us briefly a little background about why the 50 was chosen as the platform for this lens?

MS. McEACHERN: Denise McEachern, Bausch & Lomb. Bausch & Lomb currently does not produce the AT45, which is the 4.50 mm optic, so when we designed the study, we designed it with the current platform that was commercially available so that the current product could be used as a control.

DR. HIGGINBOTHAM: Dr. Owsley, did you have a question?

DR. OWSLEY: So I just want to understand your perspective on the following. So if about 1/3 -- I'll start in the affirmative -- 2/3 of the patients have 20/40 or better uncorrected at near and 1/3 is worse than 20/40 at near, in your mind, then, is it fair to say that the Trulign allows for near, intermediate, and distance vision without spectacles without also

telling the patient that it's likely a significant number will need readers for near?

DR. PACKER: This is Mark Packer. I think it's very important to let patients know that they may very well need a low-powered pair of over-the-counter reading glasses from time to time, especially for fine print.

DR. HIGGINBOTHAM: Any follow-up, Dr. Owsley? No?

Okay. Ms. Berney, did you want to comment on this question?

MS. BERNEY: Not at the moment.

DR. HIGGINBOTHAM: Dr. Leguire, did you want to comment on this question?

DR. LEGUIRE: Yes, I do. You can read me very well.

Larry Leguire. Regarding Dr. Owsley's comment, they don't say it's good vision. It simply says vision. So --

DR. OWSLEY: Can I --

DR. HIGGINBOTHAM: Yes, Dr. Owsley?

DR. OWSLEY: That's correct, and I'm partly appealing to the vagueness of the indication statement, and if indication statements are usually written vague like that, I guess that's all right.

DR. LEGUIRE: Yeah.

DR. HIGGINBOTHAM: Any other questions for the Sponsor?

(No response.)

DR. HIGGINBOTHAM: Any comments from -- oh, Dr. Bressler?

DR. BRESSLER: Just one. Given the draft description you heard of accommodation, what did you think was the best test in the future, in the near future, to determine if you meet those criteria?

MS. McEACHERN: I'd like to have Adrian Glasser come to the podium, please.

DR. GLASSER: Adrian Glasser, consultant to Bausch & Lomb. So I'd just like to say that there are many possible tests that are obviously appropriate, including pilocarpine to induce a forward shift. Doing these kinds of accommodation measurements is very difficult. It's difficult for the patients, as you can imagine. A patient under an ultrasound by a microscope with fluid on their eye making an effort to accommodate is a very challenging situation.

So the pilocarpine serves a very important role because it effectively removes variability, to some extent, from the individual patients in their ability to elicit an accommodative response. So I think there's a role. There's a very important role for including those kinds of measures in the accommodation studies to show in the case of a Crystalens that it is capable of doing what it is designed to do, namely to move forward with an accommodating effort. And certainly there are many other possible objective instruments that can be used for accommodation testing which are also appropriate.

DR. BRESSLER: And just to follow up -- Neil Bressler again --

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what do you think would be the best test to give comfort to the regulatory agencies that you meet their definition? I recognize that there are challenges in any sort of test that we may do with the patients, but what do you think would be the best test to objectively confirm it?

DR. GLASSER: So, again, you're putting me in a difficult position because I don't think there is one single test. And the ANSI standard that is being drafted does not ask for one specific instrument or one specific test. It acknowledges that there are a variety of possible ways of objectively measuring an accommodative response. So I think that that's a discussion between FDA and a sponsor to establish what is the most appropriate method.

DR. BRESSLER: Thank you very much.

DR. HIGGINBOTHAM: Any other question? Oh, Dr. Bradley?

DR. BRADLEY: A follow-up question for Dr. Glasser. One of the things that worries me, and we've heard this today, some studies seem to suggest this lens is performing as designed, as you suggested, and the ones that you presented earlier support that claim. The FDA listed numerous studies which seem to indicate that it does not perform as designed. And as one very familiar with this field, could you give us some insight as to what's the source of these dramatic differences? Is it the surgical procedures? Is it the measurement procedures? Where do these differences come from, because they're not small, they're large, I think, so --

DR. GLASSER: So I don't have a backup slide of this, but there's a very informative graph in the Marchini 2007 publication that FDA referred to. In that study, Marchini et al. identified that, in fact, there was not much accommodation measured in the AT45 patients. However, the rest of the paper provides an indication that, in fact, it really does accommodate very well. And there's a graph that shows a correlation between a movement of the ciliary body, as measured with ultrasound biomicroscopy, and a decrease in anterior chamber depth for the AT45. That's a very high correlation for the AT45.

So the inference from that graph is that the variability is coming from the individual patients in their ability to elicit a contraction of the ciliary muscle voluntarily in the experimental settings in which accommodation is being measured.

So perhaps the variability is not at all with respect to the lens or perhaps less with respect to the lens and more with respect to the variability of the patients to elicit that accommodative response.

DR. BRADLEY: Thank you.

DR. HIGGINBOTHAM: And this is Eve Higginbotham. Is there an age effect in that observation?

DR. GLASSER: The graph that is shown does not include age in it. It simply shows the relationship between the ciliary muscle movement and the change in anterior chamber depth for the AT45 patients.

DR. HIGGINBOTHAM: Dr. Feldman?

DR. FELDMAN: Following up on that point of variability from patient to patient, and you mentioned perhaps not as much of the lens, is it -- do you feel that it would be important in following up on the FDA inquiry regarding the accommodative effect of the lens to have a control with a monofocal lens to measure both the subjective and objective vision or accommodation of that lens?

DR. GLASSER: So certainly a control lens was used for the AT45 study, and I presented that in one of my slides. That was a subjective measure, and it proved effective against -- the AT45 proved effective against that monofocal control. I sense you're --

DR. FELDMAN: Yeah -- no -- and what I guess I'm getting at is in order to claim accommodation, is it important to show that it's more accommodative than a monofocal lens, which may also have some accommodation as we're defining it in some patients?

DR. GLASSER: Sure. Appropriate controls are good for clinical studies to evaluate those kinds of things, so sure.

DR. HIGGINBOTHAM: Okay. I sense we're coming to -- oh, Dr. Harris?

DR. HARRIS: Another potentially objective way to look at this would be the, like, the aberrometry that you presented for one patient, Dr. Packer. Was that technically challenging to get that patient to produce

that 1.6 diopters or something you could -- in a big study you could do a lot of people and see? You know, that's fairly objective right there. I mean, it'd be hard to fake that even if you were a biased observer, so what do you think about that?

DR. PACKER: Mark Parker. Well, I agree. And, in fact, in the ANSI draft guidance, aberrometry is one of the suggested methods for measuring accommodation. There's some tricks to it mostly related to being able to bring up an accommodative target with a machine there that might be in the way and also to avoid the effects of convergence because, you know, accommodation is really binocular. We see a lot better up close if we're allowed to use both eyes. And we'd like to get a realistic picture of that. And yet if we allow binocular fixation, then we get convergence, and now we're getting a map which is off axis because the eyes are converging. So there's some challenges to it --

DR. HARRIS: Yeah.

DR. PACKER: -- still, but I think it's one of the methods that can go toward documenting objective accommodation.

DR. HARRIS: David Harris again. The other alternative would be to take a little bit of that and just do it with 2% pilocarpine or something, do it -- take away the voluntary part of it, but just see if you can objectify that the refraction of the eye is changing in response to a -- some type of sympathomimetic drug, you know, and just leave it at that. At least you got

some idea that something is happening there that you can qualify.

DR. PACKER: I agree with Dr. Glasser also that pharmacologic stimulation is important to be able to demonstrate movement of an accommodative IOL.

DR. HIGGINBOTHAM: Okay. Any other -- Sponsor, you had something else you wanted to add?

DR. GLASSER: May I make a brief comment? One of the challenges with doing aberrometry with pilocarpine is that you get a very strong pupil constriction. And so that's typically why the biometry studies have been done with pilocarpine and not aberrometry studies.

DR. HIGGINBOTHAM: Okay. I want to remind the Panel we want to focus on the Panel questions in terms of, you know, the reason for our questions. So, Dr. Bradley, you had your hand up again?

DR. BRADLEY: It was just the discussion of the value and validity of using pilocarpine as a surrogate for measuring accommodation in the circumstance that the patient needs to invoke accommodation, that is, not when they've got pilocarpine in their eye but when they're looking at a near target. And I think to allude to the fact that the pilocarpine is an effective surrogate, I think, is misleading. Indeed, it's an extremely effective way to examine the feasibility of the mechanism, in this case, forward movement of the lens. But it is in no way a measure of whether or not the patient can actually invoke accommodation with that device, whatever the

device is, under normal circumstances, and I think therefore should not be used as a sole surrogate for the actual accommodation measurements with near fixation.

DR. PACKER: Mark Packer. I think your point is well taken. And I'd also just like to address something that you mentioned in passing when you asked Dr. Glasser about the variability that we see in some of these studies. And he pointed out that, you know, some of the measurement techniques may lead to some variability. But we've also seen in these studies something else you mentioned, which is that the surgical technique can lead to variability as well. And one of the things that we've learned over the years with the Crystalens is that a larger capsulorhexis allows for a better result. And in the Kepple study, for example, which was referenced earlier and showed essentially no or negative movement, the capsulorhexis size was quite small. And so it appears that by removing more of the anterior capsule, it allows greater flexibility of the Crystalens.

DR. HIGGINBOTHAM: Okay. Any other questions related to our Panel questions that the Panel would like to ask the Sponsor at this time?

(No response)

DR. HIGGINBOTHAM: Any final comments from the Sponsor?

MS. McEACHERN: Not at this time. Thank you.

Denise McEachern.

DR. HIGGINBOTHAM: Thank you very much for your comments

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and responding to our questions.

We are now at 3:43. I'm going to suggest that we take a 12-minute break at -- okay, I've been told we have to take a 20-minute break. It must be a Federal order.

(Laughter.)

DR. HIGGINBOTHAM: So I suppose we'll convene at 4:05.

Okay. And we're going to go through the FDA questions. Thank you.

(Off the record at 3:43 p.m.)

(On the record at 4:05 p.m.)

DR. HIGGINBOTHAM: We will call the meeting back to order.

At this time, let us focus our discussion on the FDA questions, Panel. Copies of the questions are in your folders. I would ask that each Panel member identify him or herself each time he or she speaks to facilitate transcription. If you don't, I will remind you.

Please show the first question. First question is up. Thank you.

DR. KIANG: Question 1: With regard to --

DR. HIGGINBOTHAM: Your name?

DR. KIANG: Sorry. I'm sorry. You just said that, didn't you?

(Laughter.)

DR. KIANG: Dr. Tina Kiang, FDA.

With regard to accommodative amplitude, the following information is available:

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- No objective or subjective assessments in the Trulign study
- Five subjects with 10 eyes in the original Crystalens study
- Biometry data on 31 primary eyes and push down test on 33 eyes in the Crystalens HD study
- Literature shows mixed results by objective assessments ranging from negative to positive accommodative movement

Given the currently available information, do you believe the data support the applicant's proposed indications for use of approximately one diopter of monocular accommodation?

DR. HIGGINBOTHAM: Who would like to start?

Dr. Bradley?

DR. BRADLEY: Okay. I'll start. This is Dr. Bradley. Yeah, I think I raised the point earlier that some of the tests that have been used to evaluate the Crystalens could be -- the results of those tests could be interpreted as either accommodation or some other factor such as pseudoaccommodation. And the notable tests, of course, are near visual acuity, for example, or spectacle independence. I do believe that, as we discussed just before the break, there are methods available to measure the refractive status of the eye and do that objectively and therefore evaluate whether or not the lens is accommodating.

And as has already been mentioned, with the current lens that

we're evaluating today, there has been no objective measure of accommodation established, and there are some questions developed that the original judgment that the Crystalens back in I think it was 2003 was -- the judgment that it demonstrated accommodation and it is now being brought into question. And it's been brought into question by newer experimental methods, more studies that have been done.

And I think we're now sitting in this rather difficult situation. We don't have direct evidence that this particular lens accommodates. We have no evidence, in fact, no direct evidence. And the previous, earlier version of this lens, the data that were produced at the time have been contradicted by some more recent studies, and so we're left not knowing whether we have convincing data that this particular lens can demonstrate this one diopter of accommodation. So I think we're in a bit of a dilemma.

DR. HIGGINBOTHAM: So Dr. Murray -- Bradley, how would I -- how would you actually summarize your statement? Is that a no or a maybe?

(Laughter.)

DR. BRADLEY: I think for this particular lens, it's a no, we don't have the data.

DR. HIGGINBOTHAM: Is there anyone who would like to propose another opinion or add to that opinion?

DR. STEINEMANN: It's Tim Steinemann. I struggle with this as a practitioner, and I appreciate what Dr. Bradley is saying, the scientific

assessment and refractive assessment of these parameters, but I also appreciate what Dr. Bressler said, you know, the ability to see well at a variety of distances.

But back to the practitioner's standpoint, we face on a daily basis patients who come to us, and they accept this, they want this, and they're going to get it. Don't confuse me with the facts, doctor. This is what I want, and this is what I'm going to get. And the question is are we assessing this from a scientific validity standpoint or are we looking at this from, you know, truth in advertising or, you know, is this -- are we providing a product that is living up to what we're saying it is, you know, this is an accommodating lens. I struggle with that.

DR. HIGGINBOTHAM: So as you struggle, is that a yes or a maybe?

DR. STEINEMANN: Maybe.

DR. HIGGINBOTHAM: Can we reframe the question, Dr. Eydelman?

DR. EYDELMAN: In light of Dr. Steinemann's comment, I just wanted to clarify that the question asks the Panel input specifically on accommodation, not whether this particular IOL should become available with a different, potentially, IFU, for a different indication for use. The question specifically asks is do you believe that this lens provides approximately one diopter of accommodation.

DR. STEINEMANN: It may, but it may do it for the reasons that Dr. Bradley elucidated, a variety of reasons.

DR. HIGGINBOTHAM: So it's a maybe?

DR. STEINEMANN: Maybe.

DR. HIGGINBOTHAM: Dr. Bressler?

DR. BRESSLER: Given the data that we're presented today, I would conclude the data only weakly support the possibility. And so it doesn't rule out that it might be doing that, but it's not very strong evidence, given the information that's provided. So if you had to say is there any evidence to support it, I would say yes. Does the preponderance of evidence support it? Does it support it confidently? I would say that has not been presented.

DR. HIGGINBOTHAM: Okay. Any other -- Dr. Harris?

DR. HARRIS: We have to go back -- if we go back to the FDA's definition of accommodation, though, it sort of includes the pseudoaccommodation. It doesn't really exclude -- it doesn't tell you why the patient can focus; it just says they do. And, you know, the graphs that I've seen from the Sponsor's presentation CL-9 slide, you know, shows pretty -- really good acuity at distance and intermediate.

So if you ask me whether it can reduce one diopter of FDA-approved accommodation, it seems like it does even with the other slide, which I can't find right now which looks at acuity at -- with best distance

corrected acuity at the near points. Again, as I recall, the intermediate, you know, the sort of .8 or 1 meter or whatever they used, seems like it did.

So for the definition that I've been given of accommodation by the FDA's point, I don't -- it seems to me it gets about a diopter. But, again, as you said -- we're not talking about this now -- but the label, the way it's listed there, where it states "near vision without spectacles," that's misleading, and I would be uncomfortable for that label. But whether it provides a diopter of accommodation by, you know, not the physiologic definition but by the definition the FDA's given us, it seems to me it does.

DR. HIGGINBOTHAM: Would you say it's a diopter approximately, or can you say that it just --

DR. HARRIS: Yes, yes, yeah. I'm saying, you know, if you look at their curve, it goes back -- they got acuity, the acuity of the patients, it sort of starts to drop off when it closer to -- you know, when it passes the 1 meter point. So, you know, if they can see clearly at a meter -- you know, if they're myopic, if you're not correcting for -- you know, if they're not getting their best distance correction, then you can't say that, but I believe their data showed even with that, that it was true. So I'm not saying why they seem to be able to accommodate a diopter, but the data seems to me to say that they do.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: Let me just clarify. Our definition for

accommodation does not include pseudoaccommodation, and this question is specific to accommodation alone, not to pseudoaccommodation.

DR. HARRIS: I understand that, but it seemed like to me it didn't really exclude -- didn't specifically exclude pseudoaccommodation. It just sort of said they can focus over a range, right? Isn't that what the definition said?

DR. HIGGINBOTHAM: No.

DR. HARRIS: What did it say? What --

DR. HIGGINBOTHAM: Can we have a restatement of the definition, but in the meantime, if we could have Dr. Bradley make a follow-up comment?

DR. BRADLEY: Just a follow-up comment. I really worry if we start to redefine words. I don't think we should be in that business. I think accommodation is a well-defined word. Pseudoaccommodation is a well-defined, well-accepted word. We don't need to change those definitions. They already exist. And just because the end result of those two things could be the same, that is, good near vision, doesn't mean that we can use one word when another word applies. I really believe that that would be a mistake on our part.

DR. HIGGINBOTHAM: You know, there's not a clear consensus here. So I'm going to go around the table and ask people to give me their opinions about this. I will start with Dr. Clayton.

DR. CLAYTON: I don't think we have adequate evidence to say that a diopter of accommodation, monocular accommodation, is provided by this lens.

DR. HIGGINBOTHAM: Dr. Shen?

DR. SHEN: I think we do.

DR. HARRIS: I think we do.

DR. HIGGINBOTHAM: Dr. Harris, thank you.

Dr. Owsley?

DR. OWSLEY: I think we don't.

DR. HIGGINBOTHAM: Dr. Evans?

DR. EVANS: I don't believe there's enough data to support that.

DR. HIGGINBOTHAM: Dr. Brown?

DR. BROWN: I think we do.

DR. HIGGINBOTHAM: Dr. Kim?

DR. KIM: I think we do.

DR. HIGGINBOTHAM: Dr. Bressler?

DR. BRESSLER: I don't think it supports the proposed IFU.

DR. HIGGINBOTHAM: Dr. Bradley?

DR. BRADLEY: Yeah. I don't think we have sufficient data on this particular lens.

DR. HIGGINBOTHAM: Dr. Coleman?

DR. COLEMAN: I don't think we have enough evidence at this point.

DR. HIGGINBOTHAM: Dr. Steinemann?

DR. STEINEMANN: I don't think the data supports the indication of accommodation.

DR. HIGGINBOTHAM: Dr. Feldman?

DR. FELDMAN: I think if we said one diopter of presbyopic correction, perhaps the data supports that, but as stated here, we don't have adequate evidence.

DR. HIGGINBOTHAM: Ms. Berney?

MS. BERNEY: I don't believe that the data supports the conclusion.

DR. HIGGINBOTHAM: Dr. Leguire?

DR. LEGUIRE: As the Consumer Representative, I would be hesitant to tell people it changed accommodation. No.

DR. HIGGINBOTHAM: Okay. Dr. Tarantino?

DR. TARANTINO: I think the data that Dr. Packer demonstrated on aberrometry showing a refractive change supports that there is some accommodation occurring. That said, I think it's relatively small amount, but one diopter is a relatively small amount. The question is, to me, over what size of a sample would achieve this? That's still a question that I think is not known. But, again, the point is is that when we get to these types of lenses

that are more complex and offer benefits that traditional lenses don't, oftentimes, we see that the benefit may be small. But we shouldn't downplay a small benefit. To some people, half a line, a line, could be very significant.

DR. HIGGINBOTHAM: Thank you.

Anyone who would like to add an additional comment before I attempt to summarize?

Yes, Dr. Bradley?

DR. BRADLEY: I think we have to realize that in the future, there are going to be many accommodating IOLs come before the FDA and potentially come before this Panel. And if we set the precedent here that we consider -- we muddy the water between accommodation and pseudoaccommodation, I worry about the precedent that sets for the future lenses that come our way. I don't know if that's appropriate to say that, but I do worry about that. I think we should be very clear when we say we believe this lens -- or believe that there are data to show this lens provides one diopter of accommodation. I think we should be very clear on what that means.

DR. HIGGINBOTHAM: Yes, Dr. Harris?

DR. HARRIS: David Harris. Do we have any, as part of our recommendation, can we recommend changing the name or the word for what we think this lens does? I mean, I also agree that accommodation by its

scientific definition, we're not getting that. I'm looking principally from the results. But can we make recommendations as to, well, we think it gives a diopter of something, presbyopic correction or something like that without having to use the word accommodating to -- in order to be true to our scientific roots? That's a question. I don't know what we do here.

DR. HIGGINBOTHAM: I'll turn to the FDA for that answer.

DR. EYDELMAN: You can recommend anything you want, and we will take your comments into consideration.

DR. HIGGINBOTHAM: Dr. Brown, did you have your hand up?

DR. BROWN: Yes. Jeremiah Brown. I was just going to add that, I mean, I don't think that anyone is saying that there is strong data, but there is data with the dynamic retinoscopy, there's aberration data, there's the UBM data showing the change in the anterior chamber depth. I mean, so there is some data. It's weak. But I think that that's why those of us who have said yes are saying yes.

DR. BRESSLER: One comment.

DR. HIGGINBOTHAM: Yes, Dr. Bressler?

DR. BRESSLER: Neil Bressler. So that's why I stated I don't think the data support the proposed IFU. The indication for use states that the lens provides approximately one diopter of monocular accommodation. So it's, you know, it's how you want to interpret the details of the wording.

DR. HIGGINBOTHAM: Okay. Dr. Eydeman, with regard to

Question 1, the Panel generally believes, and there was no consensus on this point, that there is some evidence that this lens provides the ability for patients to see along a continuum from near to distance, but there is no strong evidence to support the claim of one diopter of monocular accommodation.

DR. EYDELMAN: Thank you for your thoughtful deliberations of this difficult question.

DR. HIGGINBOTHAM: I'd like to offer the opportunity for revisions to my statement from any of my Panel members. I tried to summarize your thoughts. Is there anyone who strongly believes otherwise who would like to just make your own statement?

(No response.)

DR. HIGGINBOTHAM: Can we proceed to Question 2?

DR. KIANG: Dr. Tina Kiang, FDA.

Question 2: Spectacle independence was not assessed as a formal endpoint in the Trulign monocular study. At Form 4, 70.7% of toric IOL implanted eyes achieved uncorrected near visual acuity greater than or equal to 20/40, and 97.7% of toric IOL implanted eyes achieved uncorrected intermediate visual acuity greater than 20/40. The proposed indications for use states that the "...Trulign Toric provides approximately one diopter of monocular accommodation which allows for near, intermediate and distance vision without spectacles." Do you believe the available data support the

proposed indications for use?

DR. HIGGINBOTHAM: Does anyone who would like to start the discussion on this question? Yes, Dr. Bradley?

DR. BRADLEY: I have a question for the FDA. I'm a bit confused. On page -- well, on slide 70 that you presented with distance corrected near visual acuity better than -- or better than or equal to 20/40, as somebody was pointing out earlier today, these numbers are around 63, 64, 65%. In the question here, we've got around 97%. Could somebody clarify that discrepancy for me, please?

DR. KIANG: This slide is uncorrected -- Tina Kiang. This slide is uncorrected whereas the -- I mean -- excuse me -- the question is for uncorrected. The slide is distance corrected.

DR. KIM: Joung Kim. I think it's for the uncorrected intermediate is 97%.

DR. HIGGINBOTHAM: Any follow-up, Dr. Bradley? Do you see that? It's uncorrected.

DR. BRADLEY: Yeah. I think as I asked the Sponsor earlier, they indicated that the mean spherical equivalent for these patients was myopic. So clearly, if they are uncorrected, they should have better near visual acuity rather than if you're distance corrected. So maybe that's the difference between those two.

DR. HIGGINBOTHAM: Yes, Dr. Bressler?

DR. BRESSLER: Neil Bressler. My comment goes to what Dr. Eydelman said a minute ago about recommending anything you want. So before I answer the question, I just want to say I thought the statement was a little unusual for me because even if 5% had greater than or equal to 20/40 vision, it would be a true statement that the data support that it allows for near, intermediate, and distance vision. It doesn't discuss the quality of that vision, whether that's better than not using this lens, et cetera, et cetera. So it is a fact that it allows for near, intermediate, and distance vision without spectacles. That is a fact.

But I find it difficult to -- you know, what I'm implying is not written here, and what I'm implying is, you know, do the data support that that's the best way to get that or an improved way or something like that. So I just wanted to make that statement before we comment on whether the data support the proposed indication, because even if it were 5% with better than 20/40, which it wasn't, you know, yes, the data would support that it has -- it allows for vision without spectacles.

DR. HIGGINBOTHAM: Yes, Dr. Eydelman?

DR. EYDELMAN: Just to clarify. You're absolutely correct, Dr. Bressler. There is some ambiguities. The implication, however, when something is in the IFU for a new device for labeling, the implication is that that's correct for most patients that have undergone the implantation with that device.

DR. BRESSLER: So I propose that we answer the question, if you want us to, with that revision that you're talking about, for most patients, however you want to interpret most, if that's okay, Dr. Higginbotham?

DR. HIGGINBOTHAM: Dr. Bressler, I accept your amendment, but I do have a clarification. So most, is there an FDA definition for most? Like, the lawyers have preponderance of evidence, et cetera.

DR. KIANG: In the regulation, it says that the indicated population should be for the majority. That's what it says in the regulation. But there is no percentage --

DR. HIGGINBOTHAM: Does that mean --

DR. KIANG: -- in the regulation. I'm sorry.

DR. HIGGINBOTHAM: Okay. So that could be 51%?

DR. KIANG: Yes.

DR. EYDELMAN: It's what the Panel decides in their infinite wisdom the majority is.

DR. HIGGINBOTHAM: Thank you for making our jobs easier.

(Laughter.)

DR. HIGGINBOTHAM: Dr. Owsley?

DR. OWSLEY: But the way it's written there, it seems to attribute it to the -- the visual acuity to the fact that there's accommodation. So vis-à-vis, number one, we can't really -- I mean I agree with the previous

statement that for most people for near, intermediate, and distance vision without spectacles, it provides for that, but what I don't know is whether it's due to monocular accommodation.

DR. HIGGINBOTHAM: Okay. All right. I see some heads nodding. Anyone would like to offer another opinion?

(No response.)

DR. HIGGINBOTHAM: Okay. So let's try this. So, Dr. Eydelman, with regard to Question 2, the Panel generally believes that for most patients, the Trulign Toric provides or allows for near, intermediate, and distance vision without spectacles. However, the Panel could not confirm that this is related to accommodation, based on the data.

Dr. Bradley?

DR. BRADLEY: I'm just recalling a conversation that lasted for some time earlier today in which we were concerned about this notion of vision at near without spectacles and the paucity of data to support that and the lack of rigor with which that data was acquired. So it's sort of -- oh, boy, it'd be nice to have some really solid data to say yes, that's true.

And I think the Sponsor brought to our attention data from the earlier lens, which looked a lot better because they had binocular implantation and they were able to evaluate spectacle independence better. For this particular one, we're not able to do that, really, because it's a monocular implant. So, again, there are issues about this particular lens and

this claim.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: In light of Dr. Bradley's comment and the earlier discussion I believe I heard by the Panel about the assessment of spectacle independence being with not-validated questionnaire and that not being a particularly -- not being a formal endpoint, I just want to make sure I'm clear whether your statement is that the Trulign Toric provides improved near, intermediate, and distance vision or if you specifically want to say that it improves that vision without spectacles. In other words -- well, I guess I've made it clear.

DR. HIGGINBOTHAM: Dr. Feldman?

DR. FELDMAN: Just one other point that we talk about when we talk about improved -- which that word is vague to me as well. Are we talking about improved in a monofocal lens? Are we talking about improved to what they saw before surgery? In terms of eligibility for the trial, vision had to be 20/40 or worse, and now we're talking about looking at percentages of vision 20/40 or better. It seems kind of vague to me as to what is good vision versus unacceptable vision based on what we've been given here.

DR. HIGGINBOTHAM: Dr. Eydelman?

DR. EYDELMAN: I was just coming back to Dr. Higginbotham's summation, and that was -- my mere point was not to introduce another

variable or another vaguely defined term but to try to make it more precise, which obviously I've failed. I was trying to delineate whether the spectacle independence was something that the Panel agreed on or not.

DR. HIGGINBOTHAM: I believe what we heard in the discussion is that there were concerns about the lack of rigor related to validating spectacle independence. And so while I think generally the Panel agrees with the first statement, and I hope someone could reread that just to be sure we're on the same page, there were concerns about the rigor that makes it very difficult to affirm spectacle independence as a potential claim. Is that --

Yes, Dr. Steinemann and Dr. Bressler?

DR. STEINEMANN: Is it just rigor or is it design? This is a monocular trial.

DR. HIGGINBOTHAM: Good point.

Dr. Bressler?

DR. BRESSLER: There are two issues here I think that we're discussing. One is what Dr. Owsley brought up; is it from monocular accommodation. So you'd have to consider maybe you throw that part out. But if you're going to say, well, it's from something, could be monocular accommodation, could be from something else, then I thought I heard some of the experts say that, well, for many times you will need a near correction, you know, to see certain things and, you know, you certainly shouldn't advise patients to think they're never going to need spectacles for near. I think that

came up, Dr. Owsley, as you were questioning some of the people. So that has to be put into consideration in my mind as we're answering this question. So I just wanted to add that. And that's separate from this monocular accommodation issue.

DR. HIGGINBOTHAM: So I believe the concerns will be amended by the fact that we are speaking about monocular, a monocular trial, which has its limitations, just to pick up on Tim's concern about the design, so it's not just the rigor, and to also, you know, just basically consider, you know, the fact that we cannot affirm that it's one diopter based on the data. Does that --

Yes, Dr. Harris?

DR. HARRIS: Looking at this from the patients here, the citizens paying for this and so forth, the reason that someone chooses to have a lens like this on the advice of their surgeon is because they want to see better than they would have if they weren't using an accommodating or multifocal lens; the comparison is that you would have better vision -- the idea, I would think, that Bausch & Lomb would like to be true is that these patients would choose this lens -- and even though we're not supposed to consider cost, there would be some extra cost to them -- and from the safety side, we may be able to assure them that they're not going to be blinded by this lens, they're not going to be made worse by this lens than they would if they chose a standard lens. But from the effectiveness side, to be for -- in terms of

labeling or what this thing is approved for, there's some degree of is this thing better than a monofocal lens, and if so, in what way is it better? I think that we've -- I've seen some fairly good data that it's probably better than a monofocal for intermediate.

But I still have a problem with the whole near, even having near in there, because if only 60% get 20/40, and then to tell that to a patient is -- you know, if you say in one thing you're going to be able to see at near without glasses, which is what that statement says, and on the other hand, only 60% get 20/40 or better, to me, that's not so good, you know? And so I actually have a problem with the whole near part being in there; using the word near without glasses still bothers me no matter how we define accommodation or anything else.

DR. HIGGINBOTHAM: So, Dr. Harris, you're taking us into a direction of conversation about what does most mean. So I hear that you're concerned about the 60% as a measure of most. And so are you suggesting that we eliminate near from our previous statement?

DR. HARRIS: It's like I would have to eliminate the near vision without glasses thing in terms of the written indication and what would be labeled -- what the physician and the patient think is going to happen when this lens gets in someone's eye.

Background: 2004, a prolific cataract surgeon in my state, when Crystalens came out, began to promote it for the pure indication of

presbyopia because it seemed like it was going to cure presbyopia, you know? And I think he was reading the labels -- the physician was reading the labels of what this thing was supposed to do, and there were a lot of -- you know, some unhappy patients at that time because they didn't achieve, you know, kind of the degree of spectacle independence that they -- that I think he really thought he was going to provide them and that the label indicated it was, and maybe it wasn't quite that good, as I've said before. Maybe it was more like 60% and 20/40. I don't know over time if that data stood up.

But I think that on the label, on the package insert and the labeling and the indication should be, as someone said before, it should be the same for the surgeon and the patient; this is what we can expect. And, you know, I certainly, if I was putting this lens in somebody's eye, I would not tell them you're going to be able to see up close without glasses.

I'm going to say, from what I'm seeing here, I could say there's a pretty good chance you could see well at distance without glasses, pretty good chance you're going to see intermediate without glasses; probably going to need some glasses to read. And -- because my patients read medicine bottles and little newspapers and things, you know? I just would -- I would feel uncomfortable telling this patient this lens is going to make you see up close without glasses.

DR. HIGGINBOTHAM: Yes, Ms. Berney?

MS. BERNEY: Well, I can tell you that as a patient, if I knew

that that included that only 60% would get that vision, I would be very unhappy if I were not one of the 60%. I think when you make a statement like that, that's that vague, that it can't really be backed up, it's very difficult for the patient when they have surgery and it doesn't turn out the way it was supposed to. 95% of people who have LASIK get a great outcome. Well, what does that actually mean? 20/40? That's fine. I have -- right now, I'm 20/20, but I can't see. So quality of vision has something to do with that. But if I were a patient and I were paying a premium price for this and I didn't get what I thought I was going to get based on most patients see near vision, have near vision, I'd be very unhappy.

DR. HIGGINBOTHAM: Okay. Thank you.

Dr. Leguire, do you want to make a comment as a consumer?

DR. LEGUIRE: I'd simply stick with the FDA definition of majority being, you know, 51%. And I don't care what you're talking about, you know, it never applies to 100% of patients, very seldom. So I'm very comfortable with majority of patients will have good, or whatever, near, intermediate, and distance vision without spectacles.

DR. HIGGINBOTHAM: Yes, Dr. Eydelman?

DR. EYDELMAN: I just want to go on the record that I have never said 51% is majority.

(Laughter.)

DR. EYDELMAN: I was misquoted, if that was the case. The reg

specifically says that it has to be significant proportion of the patient population in order for it to make it into the IFU. So significant proportion in my personal mind is not 51%.

DR. LEGUIRE: Larry Leguire. I believe she said the majority. That's what I --

DR. KIANG: Dr. Tina Kiang. I said majority, which is basically significant percentage. I believe Dr. Higginbotham said 51% --

DR. HIGGINBOTHAM: I did. It was on me.

(Laughter.)

DR. HIGGINBOTHAM: And it was a question. I was just trying to get some clarification, but I take full responsibility.

Yes, Dr. Owsley?

DR. OWSLEY: Just to be fair to Sponsor, it's about 70%, according to the slide on the top of page 65, not 60%.

DR. BRESSLER: Neil Bressler. And then you have to decide, is that 70% a significant proportion in this population for this indication?

DR. HIGGINBOTHAM: Yes.

DR. BRESSLER: Because that may differ as well depending on what disease state you're treating.

DR. HIGGINBOTHAM: Okay. Well, I'm going to try and restate the summary and see what you guys think. So for the majority of patients, the Trulign Toric does improve uncorrected near, intermediate, and distance

vision for most patients -- I think I said that twice, so -- however, we cannot affirm that it is approximately one diopter of accommodation.

DR. EYDELMAN: Thank you. I think we can move on.

DR. HIGGINBOTHAM: Okay.

DR. BROWN: But if we use the word improve, we really should say what we're comparing -- so we should say compared to a monofocal IOL.

DR. EYDELMAN: No, we -- sorry -- Dr. Eydelman -- no, we cannot because we can only make comments about the data that's presented in the PMA. The control was accommodating IOL, not a monofocal.

Therefore, we cannot make any --

DR. BROWN: Okay.

DR. EYDELMAN: -- comparisons for which we have no data in the IFU.

DR. BROWN: Well, we could say compared to the Crystalens Accommodating IOL.

DR. EYDELMAN: Well -- Dr. Eydelman again. Then it would get us back to our comparison where that was not accurate, so --

DR. LEGUIRE: Larry Leguire, before surgery would work there.

DR. BROWN: What's that?

DR. LEGUIRE: Before surgery.

DR. BROWN: Okay. Yeah, we have to have something for the word improve. I'm just saying we can't just leave that word out there. Have

to say what's improved over what --

DR. HARRIS: You can't say improved --

DR. HIGGINBOTHAM: What would you like to say, Dr. Owsley?

DR. OWSLEY: It just allows for near, intermediate, and distant vision without spectacles for the majority of patients.

DR. HIGGINBOTHAM: Okay.

DR. OWSLEY: But we can't say it's because of accommodation.

DR. HIGGINBOTHAM: And it's not approximately one diopter?

DR. EYDELMAN: Dr. Eydelman. I think we get the gist.

DR. HIGGINBOTHAM: Okay.

DR. EYDELMAN: I think we can move on.

DR. HIGGINBOTHAM: Thank you.

DR. EYDELMAN: Thank you.

DR. HIGGINBOTHAM: Just want to be thorough. Oh,  
Dr. Bradley?

DR. BRADLEY: Yeah, I'm getting a bit worried at this point. We have two questions from the FDA. Both of the questions are basically asking us to make value judgments about the product that we're reviewing even though the data required to make the judgments were never part of the study. So we went through the first question. Did it accommodate one diopter? Well, they never measured accommodation. Now we've got a statement about spectacle lens independence, and because it was a

monocular study, they couldn't really evaluate that. So we as a Panel are in a pretty difficult situation here because you're asking us to really --

DR. EYDELMAN: Share the pain?

(Laughter.)

DR. BRADLEY: Well, no, I think you're essentially -- we have the choice to say, look, there were no data and it's done, okay? You can't make either of these statements based upon the data. Or you could say, well -- and I think this is a point the Sponsor makes, a very good point -- that this lens is essentially equivalent to one that was looked at before in which these data were included. So for both of these statements, we're in the same boat. Are we willing to accept the equivalence or are we not? Because the data are not in this study. And I think that's a trick situation to be in.

For the first one, the consensus view was we were not willing to accept the equivalence because there has been some interim studies that have brought into question the earlier data. For the reading -- sorry -- the near work spectacle independence, I don't -- nobody has brought to our attention any interim studies that have said, well, this doesn't look like that's working either. So maybe in this particular case, we can assume equivalence and go back to the original dataset. But to me, it's the same problem for both the first question and now this question. We don't have the data, so --

DR. HIGGINBOTHAM: You summarized it nicely, and I think we're just reflecting back what every Panel member has heard, and each is

making his or her own judgment based on, you know, their experience as well as their assessment of what they've heard. So that's why we spent a lot of time on the deliberations, but I certainly understand.

Okay. Any other comments on this question? And I appreciate the full discussion.

(No response.)

DR. HIGGINBOTHAM: Question 3?

DR. KIANG: Tina Kiang, FDA.

The following information is available regarding vaulting. In the Trulign Toric Accommodating IOL study, two reports in the study for P030002, Supplement 27 clinical study. For the Crystalens Accommodating IOL, one report in the original P030002 clinical study, approximately 270 MDRs potentially related to vaulting, and five cases found in the literature.

In light of this information, do you believe the data support reasonable assurance of safety of the Trulign Toric Accommodating IOL?

DR. HIGGINBOTHAM: Discussion? Dr. Shen?

DR. SHEN: This is Joanne Shen speaking. I do believe the data support the safety that --

DR. HIGGINBOTHAM: Dr. Feldman?

DR. FELDMAN: Yeah, certainly nothing is perfect, and anything we do has a possibility of having a negative outcome, but given the large number of patients in the study and the small number of serious -- this event

occurring, I think the data does support the safety of this lens.

DR. HIGGINBOTHAM: Does anyone have an opposing opinion?

DR. BRESSLER: Neil Bressler. It's relatively safe for the information we have so far, but as I note, there were five people lost to follow-up between Form 3 and Form 4. If every one of them had vaulting and were lost to follow-up and went to some other ophthalmologist for management of that, we wouldn't know. So when I'm missing data and I have these two events out of whatever it was, 71 or 91, because it included the other groups as well, then is that reasonable assurance? It's hard to say. That's all I wanted to add.

DR. HIGGINBOTHAM: Okay. Any other comments?

(No response.)

DR. HIGGINBOTHAM: Dr. Eydelman, with regard to Question 3, the Panel generally believes that the data support reasonable assurance of safety of the Trulign Toric Accommodating IOL. However, there are concerns expressed regarding missing data, patients that dropped out, and so there is also, you know, that concern.

DR. EYDELMAN: Thank you.

DR. KIANG: Tina Kiang, FDA.

Given the conduct of the study, in other words, over 400 protocol deviations ranging in severity from implantation of an unapproved device model to poor documentation procedures, do you believe that the

data generated are able to demonstrate that the benefits from the Trulign Toric Accommodating IOL outweigh the risks?

DR. HIGGINBOTHAM: Discussion? Dr. Evans? Dr. Coleman?

DR. COLEMAN: Yeah, I do believe that despite the numerous protocol deviations, I think they did look at the data and found that when they were controlling for that by the FDA, that it still was a benefit in the majority of people, so I do believe that it outweighs the risks.

DR. HIGGINBOTHAM: Does anyone have an opposing opinion?  
Dr. Bressler?

DR. BRESSLER: You asked anyone -- sorry -- Neil Bressler -- so my only caveat again is because of the incomplete follow-up, the missing data, the confidence of this one, interim analyses were done, they give me a little pause on the safety. That's all. So I forget how it was worded, but --

DR. HIGGINBOTHAM: Benefits outweigh risks.

DR. BRESSLER: Yeah, do the benefits outweigh risks. And I'd be in the probably category.

DR. HIGGINBOTHAM: Okay. Dr. Eydelman?

DR. EYDELMAN: Could I just ask Dr. Coleman to clarify what analyses she was referring to because my team is a little confused.

DR. COLEMAN: I thought they had presented some data that they had -- that I read that they had actually looked at when they didn't have -- with the deviations or they excluded the, you know, those -- they excluded

the ones with the 10 AT52 --

DR. EYDELMAN: Sponsor, not the FDA.

DR. COLEMAN: Oh, okay. Sorry.

DR. HIGGINBOTHAM: Dr. Owsley?

DR. OWSLEY: I also share the concerns that Dr. Bressler mentioned. It's hard to judge the benefits outweighing the risks because of the quality of the data.

DR. HIGGINBOTHAM: So is that a no or a maybe?

DR. OWSLEY: It's a maybe.

DR. HIGGINBOTHAM: Okay. All right. Dr. Bradley?

DR. BRADLEY: Yeah, I think in terms of the benefits, it's very clear that this toric lens does an excellent job of correcting for corneal astigmatism, and this is the true benefit of this lens. And I think they have demonstrated that very effectively.

DR. HIGGINBOTHAM: Okay. Dr. Eydelman, with regard to Question 4, the Panel generally believes that the data generated are able to demonstrate that the benefits from the Trulign Toric Accommodating IOL outweigh the risks. However, there were concerns expressed regarding the quality of the data, which puts this affirmation on some questionable grounds, but there is general consensus that the benefits are outweighing the risks. Is that adequate?

DR. EYDELMAN: Well, I just wanted to clarify. The question is

not do the benefits outweigh the risks. The question is whether the data generated are able to demonstrate. So the validity of the data, given the number of protocol deviations was the question, so I just want to make sure everybody was clear what the question was.

DR. HIGGINBOTHAM: Okay. So --

DR. BRESSLER: One comment, then. Neil Bressler --

DR. HIGGINBOTHAM: Yes, Dr. Bressler?

DR. BRESSLER: So you say general consensus; not to get on definitions here, consensus means there was a general agreement, and at least myself -- I don't want to necessarily speak for Dr. Owsley -- were questioning the confidence in the safety. And so if we don't know the safety, even though I agree with what Dr. Bradley said in terms of correcting the astigmatism, if we don't know the safety, it's hard to weigh the benefit/risk ratio. I think that's what at least the two of us are saying. So I'm not sure I would go with consensus to your statement.

DR. HIGGINBOTHAM: Okay. All right. So on that note, I'll ask each Panel member to give me their opinion. Dr. Clayton?

DR. CLAYTON: With the caveat that there is missing data, I do believe that the data generated are able to demonstrate the benefits outweigh the risks.

DR. HIGGINBOTHAM: Okay. Dr. Shen?

DR. SHEN: I stand the same.

DR. HIGGINBOTHAM: Dr. Harris?

DR. HARRIS: I agree.

DR. HIGGINBOTHAM: Could you state your agreement because this is an important point, so --

DR. HARRIS: This is to make sure what I'm agreeing to is --

DR. HIGGINBOTHAM: Yes. That's why I want you to state it.

DR. HARRIS: The risk outweigh the benefits -- I mean, the benefits outweigh the risks is what I meant to say.

(Laughter.)

DR. HARRIS: Sorry.

DR. HIGGINBOTHAM: Well, it's with the -- if you read the question, it's given that there were 400 protocol deviations, do you believe that the data generated are able to demonstrate that the benefits from the Trulign Accommodating IOL outweigh the risks?

DR. HARRIS: I do agree that the data, despite its flaws, demonstrates an adequate safety profile for me.

DR. HIGGINBOTHAM: Thank you.

Dr. Owsley?

DR. OWSLEY: Because of the over 400 protocol deviations ranging in severity, I believe that there is some concern that the data generated are able to demonstrate the benefits over the risks.

DR. HIGGINBOTHAM: Thank you.

Dr. Evans?

DR. EVANS: I actually have some of the same concerns that have been expressed. The missing data issue is an important one because there's more missing data than there are vaulting events, for example, so if people who are potentially at high risk for such events are the ones that disappear, then that becomes an issue. We don't have evidence either way about that, but the question is what sort of assumption can you make regarding that.

I think the data presented, there are some clear benefits, and based on if you can make an assumption that there's no informative censoring, meaning that what we're looking at is representative of the truth, then the benefits would outweigh the risk. But I think that's always a big assumption, which is why you have to examine why people are leaving and get as much data as you can on those people particularly in light of this case, where the prevalence of missing data is higher than the prevalence of these, you know, vaulting events.

DR. HIGGINBOTHAM: Thank you.

Dr. Brown?

DR. BROWN: Despite the protocol deviations, I do believe that the benefits of the Trulign Accommodating IOL outweigh the risks.

DR. HIGGINBOTHAM: Okay. Thank you.

Dr. Kim?

DR. KIM: Dr. Eydelman, if I could ask a question maybe. The 10 out of the 14, I guess, major deviations were implanting the 52 model. As we vote on the approval or, you know, the recommendations, will the Sponsor automatically still be able to produce a 52 model, or will that be a whole separate -- to have separate test or investigation?

DR. EYDELMAN: Only the study that was approved under the protocol and was studied is going to -- is being discussed and debated today. The others were protocol deviations. If the Sponsor ever chooses to pursue that, they would need to do an appropriate study.

DR. KIM: I think, you know, if you kind of take those out of the data, I'd be still comfortable to say, well, then what they are showing with the other minor deviations, the data generated still can show the benefits over the risks.

DR. HIGGINBOTHAM: Okay. Thank you.

DR. EYDELMAN: If -- sorry.

DR. HIGGINBOTHAM: Yes?

DR. EYDELMAN: Dr. Eydelman, if I can just comment on what you just said. There were 28 major protocol deviations, not 14. So I just wanted to make sure the numbers are correct.

DR. HIGGINBOTHAM: Do you want to maintain your statement?

DR. KIM: Yes, I still maintain the statement.

DR. HIGGINBOTHAM: Okay. All right. Thank you.

Dr. Bressler, you've already stated, but you'd like to restate?

DR. BRESSLER: Just that I cannot determine if the benefits outweigh the risk only because I can't determine the risk confidently because of the interim analyses that were done, the lack of masking of people who were measuring the primary outcomes, it's not an intent-to-treat analysis, and we're missing data, and then on top of that, some of the protocol deviations that were -- that could affect or bias the interpretation. So without that to tell me about the safety, while I appreciate the benefits, I can't do the benefit/risk ratio.

DR. HIGGINBOTHAM: Thank you.

Dr. Bradley?

DR. BRADLEY: Yeah, as far as I can tell, the protocol deviations would have very little effect on my judgment of the efficacy of this particular device. It does an excellent job of correcting corneal astigmatism, as I mentioned. The concern is whether the protocol deviations have masked some unknown risk that we are unable to judge at this point, and I think I just mirror what Dr. Bressler said. We really don't know.

DR. HIGGINBOTHAM: Thank you.

Dr. Coleman?

DR. COLEMAN: So I still believe that, despite the protocol deviations, that the benefits outweigh the risks. And I just want to point to

the Executive Summary on page 21, that there were a total of 24 major protocol deviations. On 10 of these were the wrong lenses being implanted. But if you look at the other type of major protocol deviations that are mentioned, some of them actually would swing the bias of the study to being actually where you would have a negative result, such as amblyopia patients who are admitted, incorrect keratometry values, also chronic steroid use, and also the implantation of the study lens despite anterior posterior capsular tear during surgery. So these protocol deviations actually do not change how I value the benefits versus risk.

DR. HIGGINBOTHAM: Okay. Thank you.

Dr. Steinemann?

DR. STEINEMANN: Though I share some of Dr. Bressler's concerns, I believe that the data generated do demonstrate the benefits outweigh the risk.

DR. HIGGINBOTHAM: Okay. Thank you.

Dr. Feldman?

DR. FELDMAN: I agree that while it bothers me to see the number of deviations and some data missing, that the major deviations and the large number of minor deviations don't seem to affect the primary endpoint that we're looking at, and I feel confident with the safety, given the data that's been presented.

DR. HIGGINBOTHAM: Thank you.

Ms. Berney.

MS. BERNEY: It's Berney. It's not fancy --

DR. HIGGINBOTHAM: Not Berney, sorry. I'm from New Orleans, so --

MS. BERNEY: I too have reservations regarding the number of protocol deviations, which when I was a researcher I would have called sloppy research. But I don't believe that those particular deviations would -- I don't believe that they would affect what I consider to be the benefits outweighing the risks.

DR. HIGGINBOTHAM: Okay. Thank you.

Dr. Leguire?

DR. LEGUIRE: Larry Leguire. Weighing the protocol violations with the benefits, I think it's clearly beneficial, the lens is beneficial.

DR. HIGGINBOTHAM: Okay.

And Dr. Tarantino?

DR. TARANTINO: Nick Tarantino. My assessment was very similar to Dr. Coleman's. When I was reading this, I did see that even though there were some deviations, the deviations were not in favor of the product, and therefore, I do believe that the data generated demonstrate the benefits.

DR. HIGGINBOTHAM: Okay. Dr. Eydeman, with regard to Question 4, the majority of Panel members believe that despite the 400

protocol deviations, there is reasonable assurance or some assurance that the benefits outweigh the risks of this lens. However, there was a strong minority opinion that felt that it was very difficult to be sure.

DR. EYDELMAN: Thank you.

DR. KIANG: Tina Kiang, FDA.

Below age 60, subjects implanted with the control IOL had a greater percent reduction in cylinder than those implanted with the toric IOL (1.25 diopters). In light of this, please discuss:

- a. If you believe limitations by age should be added to the indications for use; and
- b. What specific labeling recommendations you believe are appropriate.

DR. HIGGINBOTHAM: Discussion? Dr. Bradley?

DR. BRADLEY: Just for clarification, was it really established that the -- as you said, the below age 60 subjects implanted with the control IOL had greater percent reduction in cylinder? The mean I think was slightly greater, but was that a statistically significant result? Because it looks like a lot of noise at the end of a distribution with very few samples, so I'd be a bit nervous about concluding that.

DR. HIGGINBOTHAM: I'll turn it back to the FDA. Is that the correct question that we'd like to respond to?

DR. EYDELMAN: Yes. And Dr. Lu is going to make a comment.

DR. HIGGINBOTHAM: Okay.

DR. LU: Laura Lu from FDA. Here, although we mention the age 60, but really, because of the small size in that subgroup, we cannot really make any statistical statement there. But I think we are aiming to say that there's the -- really the treatment effect, relative treatment effect decreases as age decreases, so whether there is any recommendation from you for the appropriate language.

DR. BRADLEY: I thought I knew what you were trying to say, but this statement that we're going to respond to doesn't say that. It just says that the subjects implanted with the control IOL had greater percent reduction, so maybe that needs to be modified --

DR. LU: Yeah, we would say be observed.

DR. BRADLEY: Yeah.

DR. HIGGINBOTHAM: So just to clarify, you want to change it to less reduction?

DR. HILMANTEL: Gene Hilmantel, just to clarify, so the point estimate for that segment of patients under age 60, the percent reduction was as indicated in the question here. But there wasn't an analysis that showed that that was statistically significant for that age group, okay? So in the few patients below age 60, the control had better results than the toric in the randomized part of the study --

DR. EYDELMAN: Dr. Eydelman. Did that clarify, or you need

further clarification?

DR. BRADLEY: Well, I'm just looking at the graph that's slide 92, and we have two overlapping distributions below age 60. I think the conclusion I would draw from that is the two datasets are indistinguishable in that range. The means might be slightly different, of course, they have to be, but the datasets are not -- well, they just look to me -- if I pooled everybody from 60 on down, I can't believe that's a statistically significant difference. So I would use the word indistinguishable rather than greater than.

DR. HILMANTEL: Gene Hilmantel. Excuse me. Yeah, Dr. Bradley is correct. I mean, it's just the -- it's the overall trends that are significant there. And so it's just the observed values in which the control does better below age 60, but that certainly is not significant. There is significant overlap, as Dr. Bradley said.

DR. HIGGINBOTHAM: So, Dr. Bradley, since you have the floor, would you like to offer an answer to this question?

DR. BRADLEY: I gave an indication earlier about the problem with these data, that this is a percentage. And as you'll see, some of the control eyes had 100% correction of their astigmatism, which seems very unlikely unless the astigmatism was a very low amount and the procedure itself introduces a slight astigmatism.

So as presented as percentages, it's very difficult for us to make much sense of this graph. It really needs to be presented in diopter

terms before any real decision can be made.

DR. HIGGINBOTHAM: So I take it that you're not suggesting there should be any limitations?

DR. BRADLEY: Um-hum.

DR. HIGGINBOTHAM: Okay. By age?

DR. BRADLEY: Yeah.

DR. HIGGINBOTHAM: Is there anyone who feels there should be limitations based on age? Yes, FDA?

DR. EYDELMAN: Sorry. I believe Gene has another clarification for --

DR. HILMANTEL: I'm sorry. I just want to address Dr. Bradley's comment. So that graph is actually completely equivalent to dioptric results in which 100% is equal to 1.33 diopters. The intended correction was always 1.33 diopters for the randomized portion of the study. So on the y-axis, 100% is always that, so that's completely equivalent.

DR. HIGGINBOTHAM: Dr. Bradley, does that clarify?

DR. BRADLEY: Well, it just surprises me that the non-toric IOLs, many of the eyes have pretty much a full correction, if I'm reading that graph correctly, which is interesting.

DR. HIGGINBOTHAM: It's possible, because it was less than 1.25, and just making the incision can -- in a particular -- in the steep axis can actually reduce astigmatism.

Yes, first, Dr. Harris, then Dr. Shen?

DR. HARRIS: Just on that, David Harris speaking. The lower end of that group may have only had .83 diopters of a cylinder, and they've stated that their surgically induced astigmatism averaged .7, so right there, you know -- and if you had a little extra, some of those people had, you know, 2 diopters of surgically induced astigmatism, so when it's low end, you can expect to see that scatter, I would think.

DR. HIGGINBOTHAM: Dr. Shen?

DR. SHEN: That's what I was going to say. Remember there was a graph about the range, and some of those patients had 3 diopters of surgically induced astigmatism.

DR. HIGGINBOTHAM: Okay. Is there anyone who would like to offer a proposal that there should be limitations by age?

Dr. Leguire?

DR. LEGUIRE: Regarding the lower age limits in the toric lens, no. Based on the data, I would have to say there may be some limitations of use of the mono lens above the age of 70 or so.

(Laughter.)

DR. HIGGINBOTHAM: Based on the Trulign. Okay. Hearing no affirmations related to my statement, I'm going to state, in summary, Dr. Eydelman, in answer to Question No. 5, the Panel generally believes that there should not be any limitations by age added to indications for use, and

there are no specific labeling recommendations, therefore, that we are proposing. Is that adequate?

DR. EYDELMAN: Yes. Thank you.

DR. HIGGINBOTHAM: Okay. Yes, Dr. Leguire?

DR. LEGUIRE: Larry Leguire. Just one clarification. This doesn't mean you're approving it for pediatric use, just in adults above the age of --

DR. HIGGINBOTHAM: Don't make our job more difficult.

(Laughter.)

DR. HIGGINBOTHAM: Okay. Question No. 6?

DR. KIANG: Tina Kiang, FDA.

Before I read this question, I'd like you to please be reminded that the inclusion of a post-approval study question should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risk outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and benefit before the device can be found approvable and any post-approval study should be considered.

Leading into Question 6: Please discuss if there is a need for postmarket evaluation of the real-world device performance, including:

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- Appropriate study questions and study design
- Safety and effectiveness endpoints
- Appropriate follow-up for long-term evaluation and
- Need for evaluation of performance in subgroups.

DR. HIGGINBOTHAM: Discussion?

Dr. Bressler?

DR. BRESSLER: I would like to have a small cohort where a good effort is made to see if accommodation is really being done in this by the various methods that the Sponsor and the FDA agree would be feasible and would help tell that. I'd like a large number of people with a short follow-up to understand this vaulting information because I don't believe we have adequate numbers to know what that risk is so far in the short run. And then I'd like to see a small cohort followed in the long run because I'm not certain that what looks safe at a year is necessarily safe several years later. That's much harder to do. I understand. I'm just saying, if feasible, and what could get discussed between the Sponsor and FDA, that would be important because these lenses do stay in forever.

DR. HIGGINBOTHAM: Dr. Owsley?

DR. OWSLEY: I would like to see patient reported outcome data collected with a validated questionnaire.

DR. HIGGINBOTHAM: Dr. Feldman?

DR. FELDMAN: I would like to see efficacy in binocular

implantation.

DR. HIGGINBOTHAM: Dr. Brown?

DR. BROWN: And along with monitoring for the vaulting, also just monitoring stability of the positioning of the lens along the lines of what Dr. -- was just mentioning.

DR. HIGGINBOTHAM: So linking positioning with outcomes?

DR. BROWN: Yes.

DR. HIGGINBOTHAM: Yeah.

DR. BROWN: Actually, more in terms of just safety.

DR. HIGGINBOTHAM: Okay.

DR. BROWN: In terms of is there any lens shift going on in later years.

DR. HIGGINBOTHAM: Okay. Any other comments?

(No response.)

DR. HIGGINBOTHAM: Is there anyone who does not feel there should be a postmarket study?

(No response.)

DR. HIGGINBOTHAM: Okay. Dr. Eydelman, in response to Question 6, the Panel generally believes that there is a need for postmarket evaluation of the real-world device performance, including all the components outlined in the question, but more specifically, there is an interest in seeing a pilot study to validate accommodation using objective

measurements; a large study to further assess the vaulting adverse event; a small cohort to determine some of the long-term adverse events beyond -- there was no particular timeframe stated -- beyond six months?

DR. BRESSLER: Yes. But I really -- I don't want to corner either the Sponsor or the FDA with that. I'm saying that the lens is in there for a long time. Changes can happen as fibrosis of the capsule, et cetera, occurs, and so I think, you know, it needs to be addressed longer term.

DR. HIGGINBOTHAM: Okay. There is also an interest of patient-reported outcomes particularly related to satisfaction, efficacy in the binocular insertion of this lens, and greater monitoring regarding the positioning of the lens as it relates to safety.

Did I miss any specific points from -- yes, Dr. Harris?

DR. HARRIS: I think you may have said it, but just to make sure, I think it's very important as Dr. Bradley said to have some rigorous looks at the accommodation part of it; you know, if the lens is approved, look at long-term, is there some kind of accommodation going on here or not so we can in the future, like you said, not set a precedent calling a -- using a non-scientific term for accommodation. And I think it may matter like, if other technologies come along in which there's true deformation of an artificial lens or some other mechanism to alter the refractive, you know, index of -- on the fly. All these other things that could come down the line, I think FDA should adopt a definition of accommodation that's equivalent to what's in the physiology

textbook.

DR. HIGGINBOTHAM: So, Dr. Harris, my first bullet was pilot study to validate accommodation, but you bringing up the importance of a temporal follow-up, following these patients for long-term to assess the sustainability of the accommodation effect?

DR. HARRIS: That and also just to, you know, to establish -- you know, to have some -- I think that there's a great deal of confusion as to what this lens is doing, if it's doing something better than a monofocal lens does. And with this lens, another study could answer that question and at the same time establish precedent for what we're calling accommodation, you know? I mean, what are we going to call it when somebody presents a lens which, you know, vibrates and changes its refractive index or if somebody -- and inflates the bag with a gel? Is that accommodation, you know? I'd like to come up with -- not me personally, but have a definition of accommodation which would sort of fit -- somewhere fit with what's going on in the normal human eye, and then maybe have to have a different word for what it is, you know, what these lenses do. If it's vibrating and changing its refractive index, that's not accommodation in the sense of human accommodation.

DR. HIGGINBOTHAM: Okay.

DR. HARRIS: So I would just like to maybe have somebody look at the definition of these terms. And if we're going to call a lens an accommodation lens, what does that mean? I really don't know yet.

DR. HIGGINBOTHAM: So you're speaking to the standards that goes beyond this lens, and so --

DR. HARRIS: Yeah, yeah.

DR. HIGGINBOTHAM: So I think FDA has heard that and is working on that very point.

Dr. Eydelman?

DR. EYDELMAN: So I have a number of comments in light of what I just heard. Where should I start? I just want to -- if you can flash the preface to this question?

DR. KIANG: Sorry. I didn't have it on here. I would have to pull up Megan's slides.

DR. EYDELMAN: Okay. So what Dr. Kiang read into the record prior to putting the question up is -- was a reminder that the inclusion of the post-approval study questions should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits.

So I just wanted to make sure that all of the comments that we just heard were meant to be for post-approval consideration, especially I was concerned about studying its accommodative ability. In other words, if you approved an accommodating IOL, you're assuming that it's accommodating.

If you didn't approve accommodating IOL, then you don't have anything to study in a postmarket study. So we sort of get into this circular logic, which doesn't work. So that was one of the comments I had.

Then with regard to the confusion about definition of accommodation, as far as we're concerned, there's really no confusion. We're very clear that accommodation is really what the physiology textbooks mean by accommodation, what the ANSI provides a definition for what accommodating IOL is, and I can read it again, and it took ANSI committee quite a while to come up with it. So I think those who have been involved are pretty married to this definition.

ANSI currently defines AIOLs as those that provide vision over a continuous range of distances by effecting a change in the vergence power of the eye resulting from the implant design that changes eye optical power or implant position in response to a stimulus.

So that basically mirrors what the physiological accommodation is. So as far as we're concerned, there's really no confusion about the definition. And I think I'll stop here for now.

DR. HIGGINBOTHAM: Well, we can remove that first bullet, which is the validation if Dr. Bressler accepts that recommendation since that was his recommendation.

DR. BRESSLER: I was thinking, you know, does it add to the safety and understanding of what's going on. So assuming that it's approved

for accommodation with the data that we've been provided, which may not meet your definition, but I'm being asked assuming it's approved with the word accommodation, I need other definition, I think, to help, as a physician, know where I want to use this because it's inadequate information, as we had consensus, that it seems to meet that definition. So a circular answer to your circular question.

DR. EYDELMAN: Point taken.

DR. HIGGINBOTHAM: I think this reflects some of the grayness that we're working within as it relates to this issue.

So is that adequate, Dr. Eydelman?

DR. EYDELMAN: Adequate enough to move on to voting questions.

DR. HIGGINBOTHAM: Okay. At this time, the Panel will hear summations, comments, or clarifications from FDA.

FDA, you have five minutes.

DR. EYDELMAN: I just wanted to thank the Panel for a very thoughtful discussion. I was very impressed with the number of questions for both the FDA and the Sponsor, and hopefully, we've provided adequate discussion and answers to help you formulate your voting question.

And I also want to take this opportunity to thank our colleagues from the Office of Surveillance and Biometrics who have done an enormous amount of work in support of this Panel as well as my team, which

has spent enumerable hours working on this presentation.

DR. HIGGINBOTHAM: Thank you. Any other comments from FDA? No? By head nod, I see that we're moving on.

At this time, we will hear summations, comments, or clarifications from the Sponsor. You also have five minutes. And FDA will leave the table, and Sponsor will return to the table for five minutes.

DR. PACKER: Thank you. Mark Packer, consultant to Bausch & Lomb. Well, let me say if the elephant in the room is accommodation, I share your frustration because this study was never designed to prove accommodation. This study was designed to prove the correction of astigmatism by a toric optic that was added to an accommodative intraocular lens parent platform. And I would just like to remind you all as scientists that absence of evidence is not evidence of absence.

I hope that Dr. Glasser and I were able to share with you some of the important data that has been collected in the decade since the approval of the AT45, which has, in some instances, given strong support to the notion that this lens really moves in the eye, including the study which was submitted in support of the submission of the HD-100 lens using pharmacological means to demonstrate movement, including the Macsai study, which was the largest of the studies shown, which although used a semi-subjective method of dynamic retinoscopy did involve masked observers and did show a significant accommodative effect.

I'd also like you to consider strongly the evidence that shows clinical subjective evidence of accommodation, and I think we've all seen that in our practices, and showed it again today that between infinity and a meter, the vision is comparable with the Crystalens, and within a meter, at intermediate distance, at 80 cm, we're still seeing 20/20 vision in those who have 20/20 at distances.

I agree completely with the concerns of the Panel that near vision is not uniform in Crystalens patients and that many will need a low-powered reading add, an over-the-counter pair of glasses that's 1.25 or 1.50. That's the clinical reality.

I hope that you will give due consideration to allowing this product to maintain its labeling for accommodation because I don't think there is any doubt that the clinical reality is that it is at least correcting presbyopia. The question is how is it doing it and what portion of that, as Dr. Bradley mentioned, is true accommodation, a real change in vergence power of the eye, and what portion of that may be other mechanisms.

Dr. Bradley, in one of his papers, points out that accommodation is more broadly defined as a change in refractive power of the eye, and we might better consider that as the full refractive power and not limit ourselves to spherical equivalent but consider higher order aberrations as well. Some part of the function of the Crystalens may involve spherical aberration, may involve depth of focus.

But I would submit to you that the evidence supports that at least a preponderance of its mechanism involves true change in vergence power of the eye by axial movement. It's been demonstrated in clinical studies. It's been shown by UBM, which is not easy to obtain. It's been shown by wavefront aberrometry. And it's certainly reflected in the clinical data.

But enough about accommodation, because this trial was never designed to prove anything about accommodation. I'd rather talk about the safety of this lens, which met all of the ISO and FDA grid standards. And I'd like to talk about the effectiveness of this lens in terms of correcting astigmatism, because it does a beautiful job. The mean uncorrected distance visual acuity was 20/25, and there was a significant difference between the treatment and the control group. I understand the concerns about age, but I don't think there's a medical rationale to explain that.

We saw almost 86% reduction in cylinder. We saw outcomes better than the market leader today, the AcrySof Toric. And we saw a high percentage within .50 and within 1 diopter of intended with a mean residual cylinder of less than .50 diopters in all the groups. Eighty-four percent had uncorrected vision within two lines of best corrected, and 64% had uncorrected within one line.

These are the real-world benefits that our patients will enjoy with this lens. I've been using a lens like this for over a decade, but I've been

frustrated because I have to do additional procedures to correct astigmatism to get the benefit out of this lens. By introducing a toric optic on a proven accommodative platform, we can avoid having to make corneal incisions. We can avoid having to do enhancement procedures with the excimer laser. We can give our patients a better result with a single safer procedure.

Thank you very much for your consideration.

DR. HIGGINBOTHAM: Thank you. Before we proceed to vote, I will ask our non-voting members, Dr. Larry Leguire, our Consumer Representative, Dr. Tarantino, our Industry Representative, and Ms. Berney, our Patient Representative, if they have any additional comments.

I'll ask Ms. Berney to go first.

MS. BERNEY: I just want to thank this Panel and the Sponsors for the information presented today. I do a lot of panels, and I think this is one of the more spirited Panel discussions that I have attended, and I have learned an enormous amount today. And any time I can do that, I'm happy. So thank you all for your participation and for having me here.

DR. HIGGINBOTHAM: Thank you for your input.

Dr. Leguire?

DR. LEGUIRE: Larry Leguire. I do believe that the Trulign Toric Accommodating IOL lens is an improvement of what's out there presently. I think that's clearly shown by the data.

The concerns are, however, and these may be historical

concerns, about accommodation. But, nonetheless, it is a very safe product I feel, and I think it's a well-tolerated product. And I do think it does the job that it's intended to do. I hate to have it withheld simply because of semantics perhaps or not clearly defining the mechanism of action. And I do see some converging lines of evidence which are important in supporting the possibility of accommodation of this lens.

And so when I talk to Lions members throughout Ohio anyways, and with the average age of 75, if they haven't had cataract surgery, they'll probably plan to have it soon. And so with those consumers, personally, I would have no problem recommending this lens. The problem I would have is saying that it's going to improve your vision because of accommodation.

DR. HIGGINBOTHAM: Thank you.

Dr. Tarantino?

DR. TARANTINO: Nick Tarantino. I have no additional comments. Thank you.

DR. HIGGINBOTHAM: Thank you. We are now ready to vote on the Panel's recommendation to FDA for the Trulign Toric Accommodating Posterior Chamber Intraocular Lens. Those questions are in your folders, Panel, so you can take them out now.

The Panel is expected to respond to three questions related to safety, effectiveness, and benefit versus risk. Ms. Facey will now read three

definitions to assist in the voting process, and I encourage you to listen very, very carefully. Ms. Facey will also read the indication statement for this product.

MS. FACEY: The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

The definitions for safety, effectiveness, and valid scientific evidence are as follows:

Safety, as defined in 21 C.F.R. Section 860.7(d)(1) - There is a reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risk.

The definition of effectiveness, as defined in 21 C.F.R. Section 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant

portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against any unsafe use, will provide clinically significant results.

Definition of valid scientific evidence, as defined in 21 C.F.R. Section 860.7(c)(2) - is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

The Sponsor has proposed the following indications for use:

The Trulign Toric Accommodating Posterior Chamber Intraocular Lens is intended for primary implementation in the capsular bag of the eye for the visual correction of aphakia and postoperative refractive astigmatism secondary to removal of a cataractous lens in adult patients with or without presbyopia who desire improved uncorrected distance vision and reduction of residual refractive cylinder. The Trulign Toric Accommodating Posterior Chamber Intraocular Lens provides approximately one diopter of monocular accommodation, which allows for near, intermediate, and

distance vision without spectacles.

The following questions relate to the approvability of the Trulign Toric Accommodating Posterior Chamber Intraocular Lens. Please answer them based on your expertise, the information you reviewed in preparation for this meeting, and information presented today.

Panel members, please use the buttons on your microphone to place your vote of yes, no, or abstain to the following three questions.

Voting Question 1: Is there reasonable assurance that the Trulign Toric Accommodating Posterior Chamber Intraocular Lens is safe for use in patients who meet the criteria specified in the proposed indication?

Please vote now: yes, no, or abstain.

(Pause.)

MS. FACEY: Okay. Voting Question No. 2: Is there reasonable assurance that the Trulign Toric Accommodating Posterior Chamber Intraocular Lens is effective for use in patients who meet the criteria specified in the proposed indication?

Please vote now: yes, no, or abstain.

(Pause.)

MS. FACEY: And the final voting question, Voting Question No. 3: Do the benefits of the Trulign Toric Accommodating Posterior Chamber Intraocular Lens for use in patients who meet the criteria specified in the proposed indication outweigh the risks for use in patients who meet

the criteria specified in the proposed indication?

If you would please vote now: yes, no, or abstain.

(Pause.)

MS. FACEY: Okay. The three voting questions are now complete. If you could give me a minute just to verify the votes.

(Pause.)

MS. FACEY: Okay. Thank you for those couple of minutes.

On Question No. 1, the Panel voted 10 yes, 0 noes, 2 abstains that the data shows that there is reasonable assurance that the Trulign Toric Accommodating Posterior Chamber Intraocular Lens is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 10 yes, 1 abstain, 1 no that there is reasonable assurance that the Trulign Toric Accommodating Posterior Chamber Lens is effective for use in patients who meet the criteria specified in the proposed indication.

I'm sorry. Can I have one minute, please?

(Pause.)

MS. FACEY: Okay. I'm sorry about that. I just wanted to, again, confirm before I stated anything into record. So, again, on Question 2, the Panel voted 10 yes, 1 abstain, 1 no that there is reasonable assurance that the Trulign Toric Accommodating Posterior Chamber Intraocular Lens is effective for patients who meet the criteria specified in the proposed

indication.

And the final voting question, Question No. 3, the Panel voted 10 yes, 1 no, 1 abstain that the benefits of the Trulign Toric Accommodating Posterior Chamber Intraocular Lens do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

DR. HIGGINBOTHAM: Okay. The three voting questions are now complete. I will now ask the Panel members to discuss their votes. If you answered no to any question, please state whether changes to labeling, restrictions on use, or other controls would make a difference in your answer.

I'll start with Dr. Feldman.

DR. FELDMAN: Do you want to only discuss if we've voted no?

DR. HIGGINBOTHAM: Well, state why you voted the way you did --

DR. FELDMAN: Okay.

DR. HIGGINBOTHAM: -- basically, in a summation would be fine. You don't have to go question by question.

DR. FELDMAN: Yeah. I think the preponderance of the data and evidence that we were given shows the efficacy and safety of the lens for the proposed patient population and indication.

DR. HIGGINBOTHAM: Thank you.

Dr. Steinemann?

DR. STEINEMANN: I agree.

DR. HIGGINBOTHAM: Dr. Coleman?

DR. COLEMAN: Yes. I voted yes for all three, too, with the assumption, though, that the FDA would address the labeling on the one diopter of monocular accommodation.

DR. HIGGINBOTHAM: Thank you.

Dr. Bradley?

DR. BRADLEY: I abstained on Question No. 2 because the indications as they were read indicated two indications. One was to correct corneal astigmatism and treat aphakia, and for that, the answer would be yes. The other one was to provide one diopter of accommodation, and for that, the answer was no. So I didn't get the choice of yes and no, so I voted to abstain.

DR. HIGGINBOTHAM: Thank you, Dr. Bradley.

Dr. Bressler?

DR. BRESSLER: I voted to abstain on the safety issue because of my concern of having inadequate safety information when an interim analysis was done and when there wasn't masking of the people assessing the outcome. And the protocol deviations were the least influential on that decision.

I voted yes on number 2. I thought it was effective for reducing the cylinder.

And for number 3, I abstained again because without adequate

information for the safety, I couldn't make a judgment on the risk/benefit ratio.

DR. HIGGINBOTHAM: Thank you, Dr. Bressler.

Dr. Kim?

DR. KIM: I agreed for all, said yes for all three. I do think we expressed our concerns regarding the labeling and the accommodation issue, but I did vote yes for all three.

DR. HIGGINBOTHAM: Thank you, Dr. Kim.

Dr. Brown?

DR. BROWN: I voted yes on all three. I felt that the lens was found -- or there is reasonable assurance that the lens is safe. I do think that an aftermarket study would be helpful for advising future use of the lens in knowing indications that might not be as advantageous. I did feel that it was effective in accomplishing the goals that it purports to accomplish and that the benefits outweigh the risks.

DR. HIGGINBOTHAM: Thank you.

Dr. Evans?

DR. EVANS: I abstained from the safety question for some of the same reasons that have been expressed, and I felt that more clinical experience would be better suited to answer that question.

I voted no on both questions 2 and 3 for concerns for trial quality, primarily around unplanned interim analyses, many protocol

deviations, and loss to follow-up and other trial quality issues.

DR. HIGGINBOTHAM: Thank you.

Dr. Owsley?

DR. OWSLEY: I voted yes on Question 1 because I felt there was reasonable assurance of safety. I voted yes on Question 2 because I felt there was reasonable assurance of effectiveness. And I voted yes on Question 3 because I thought the benefits outweighed the risks.

DR. HIGGINBOTHAM: Thank you.

Dr. Harris?

DR. HARRIS: David Harris speaking. I voted yes for all three questions. Essentially, I believe there's been a 10-year experience with this or a similar lens that the main change is simply the astigmatic correction which I thought was done well and demonstrated well, and I felt that the labeling questions could be addressed later.

DR. HIGGINBOTHAM: Thank you.

Dr. Shen?

DR. SHEN: Joanne Shen speaking. I voted yes for all three questions, and as my previous Panelists have stated, I agree with them.

DR. HIGGINBOTHAM: Thank you.

Dr. Clayton?

DR. CLAYTON: I voted yes for all three, with the caveat that concerns related to the labeling have been well-expressed by the Panel and

with encouragement that there be postmarket studies that would specifically include patient-reported outcomes so we can understand how patients with astigmatism respond to this first-of-a-kind implant. I think that's going to be particularly important, and there really is a dearth of data in that regard at the present time.

DR. HIGGINBOTHAM: Thank you.

I would like to thank the Panel, FDA, and the Sponsor for their contributions to today's Panel meeting. I think I've been working on this Panel for more than a decade, and I would have to agree that this has been one of the most spirited discussions. I would really agree with you, Ms. Berney. And I'd like to certainly thank Panel and Sponsor for -- or the FDA and the Sponsor for providing us the fodder for this conversation that we had today. It was a good, deep conversation.

So Panel members, it's been wonderful working with you today. Thank you for your attention.

I'd like to particularly thank our Patient Representative, Ms. Berney; our Consumer Representative, Dr. Leguire; and our Industry Representative, Dr. Tarantino, for your contributions.

Dr. Eydelman, do you have any final remarks?

DR. EYDELMAN: Thank you, and safe travels home.

DR. HIGGINBOTHAM: Okay. The April 8th, 2013 meeting of the Ophthalmic Devices Panel is now adjourned. Thank you.

(Whereupon, at 5:47 p.m., the meeting was adjourned.)

CERTIFICATE

This is to certify that the attached proceedings in the matter of:

OPHTHALMIC DEVICES PANEL

April 8, 2013

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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CATHY BELKA

Official Reporter