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P R O C E E D I N G S

8:13 AM

DR. MC CULLEY: I will call the meeting to order. I would like to turn the floor to Ms. Thornton.

MS. THORNTON: Good morning, and I would like to welcome all the attendees. Before we begin with today's agenda, I have a few short announcements to make. I would like to remind everyone that you are requested to sign in on the attendance sheets in the registration area just outside the meeting room.

You may pick up an agenda and information about today's meeting, as well as tomorrow's meeting and how to obtain summary minutes or Panel transcripts. You should make a note that there is a Panel meeting tentatively scheduled for September 23, 1999.

Information will be on our web site as soon as it can be put up. Messages for Panel members and FDA participants, information or special needs should be directed through Ms. Amory Williams or Ms. Theresa Lewis who are available at the registration table.

For those of you with cell phones and pagers we ask that you turn them off or put them in the vibration mode. Lastly, will, not exactly lastly, will all meeting participants please speak into the microphone and give your name clearly so that the transcriber will have an accurate

recording of your comments.

For those of you who will be making presentations at the presentation table, this includes FDA staff, there are name tents on the tables. You cannot see them, but pick out whatever name you like and put it up when you prepare to make your presentation.

There will be possibly if time allows some network news filming during the open public hearing portion of the meeting and possibly a little bit further into the meeting. I just wanted you to be aware of that, and now, I would like to extend a special welcome to the Panel and to express FDA's appreciation to them for the time they have taken from their busy schedules to prepare for this meeting. This has been a pretty hefty load of documents for everyone to go through, and they have all done very well, I am sure, and I really want to thank them for the effort that they put forth to prepare for us today.

I would like to have the Panel now introduce themselves for the record, beginning with Dr. Marcia Yaross.

DR. YAROSS: Marcia Yaross. I am director of regulatory affairs at Allergan in Irvine, California and industry representative to the Panel.

MS. MORRIS: I am Lynn Morris, California State Department of Consumer Affairs, Deputy Director.

DR. FERRIS: I am Frederick Ferris, Director, Division of Biometry and Epidemiology, National Eye Institute.

DR. VAN METER: Woody Van Meter, private practice in cornea and external disease in Lexington, Kentucky.

DR. MACSAI: Marian Macsai, professor of ophthalmology, West Virginia University School of Medicine.

DR. JURKUS: Jan Jurkus, professor of optometry, Illinois College of Optometry.

DR. HIGGINBOTHAM: Eve Higginbotham, professor and chair, Department of Ophthalmology, University of Maryland, School of Medicine.

DR. PULIDO: Jose Pulido, professor and head, Department of Ophthalmology, University of Illinois.

DR. MC CULLEY: Jim McCulley, professor and chairman, University of Texas, Southwestern Medical School.

DR. SUGAR: Joel Sugar, professor of ophthalmology, University of Illinois, Chicago.

DR. BULLIMORE: Mark Bullimore, associate professor, Ohio State University, College of Optometry.

DR. MATOBA: Alice Matoba, associate professor of ophthalmology, Baylor College of Medicine.

DR. MANNIS: Mark Mannis, professor of ophthalmology, University of California, Davis.

DR. WANG: Ming Wang, Director of Refractive Surgery, Vanderbilt University.

DR. ROSENTHAL: Ralph Rosenthal, Division Director, Division of Ophthalmic Devices.

MS. THORNTON: Thank you, everyone. I would like to now read the conflict of interest statement for the Ophthalmic Devices Panel meeting for July 22. The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of an impropriety.

To determine if any conflict existed the agency reviewed the submitted agenda and all financial interests reported by the committee participants. The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employer's financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved is in the best interests of the government.

A waiver has been granted for Dr. Ming Wang for his interest in a firm that could potentially be affected by the Panel's deliberations. Copies of this waiver may be obtained from the agency's Freedom of Information Office,

Room 12A-15 of the Parklawn Building. We would like to note for the record that the agency took into consideration certain matters regarding Drs. Mark Bullimore, Frederick Ferris, Janice Jurkus, Marian Macsai, Mark Mannis and Ming Wang. These individuals reported past and/or current interest in firms at issue but in matters not related to today's agenda.

Therefore the agency has determined that they may fully participate today. The agency, also, considered Dr. Michael Grimmet and Dr. Mark Mannis' reported involvement related to vision correction. In the absence of any financial interests the agency has determined that they may participate fully in today's deliberations.

In the event that the discussions involve any other product or firms not already on the agenda for which an FDA participant has a financial interest the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record.

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

Thank you, and I would like to now read the

appointment to temporary voting status for today's meeting. Pursuant to the authority granted under the Medical Devices Advisory Committee charter dated October 27, 1990, as amended April 20, 1995 and October 10, 1997, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for the duration of this meeting on July 22, 1999, Drs. Frederick Ferris, Mark Mannis, Woodford Van Meter, Alice Matoba, Ming Wang.

I, also, appoint Dr. Michael Grimmert as a voting member of the Panel for the discussion of the homium(?) laser for the correction of hyperopia. For the record these persons are special government employees and are consultants to this Panel or consultants or voting members of another Panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This appointment order was signed by Dr. David W. Feigel Jr., Director of the Center for Devices and Radiological Health, July 21, 1999.

Thank you, Dr. McCulley.

DR. MC CULLEY: We will now begin the open public hearing. This is a 30-minute session. There have been three individuals who have stated prior to the meeting that they wished to speak and have been allotted time. Time allowing

in this 30-minute session, others will be recognized to speak. I am not allowing, I will make note for you that there will be another 30-minute session for open public hearing near the end of the Panel's deliberations. So, the clock will be running.

Each of the individuals who has been allotted time has been allotted 10 minutes maximum.

Dr. Stonecipher?

Please identify yourself and any interests, financial interests, ties that you might have?

DR. STONECIPHER: Good morning. I am Dr. Carl Stonecipher. I feel very honored to have this opportunity to speak before this Panel with regard to data for laser in situ keratomileusis. It has been a pleasure to work with this group of individuals over the past 3 years and finally see these endeavors come to fruition. I have no vested interest in either the company's laser technologies that we are looking at nor other industry-related conflicts that I think would interfere with my presentation to this Panel.

I do serve as a clinical adviser to Laser Vision Center's, but I am not currently paid consulting fees from them other than travel reimbursement to and from meetings regarding those consultations.

I have been associated with refractive surgery

since its inception in the US with the National Eye Institute's initial radial keratotomy trials. As a medical student, I helped collect data for these trials for one of the investigators. I have had the opportunity to work with the Excimer laser starting with bench-top models back in the late eighties. I was first exposed to the VISX and Summit lasers in clinical trials in the late eighties as well. I have participated in a peripheral role in data collection for these trials, as well as watched these lasers come to approval in 1995.

I started my research career as a student at Southern Methodist University. My first exposure to FDA-oriented trials was as a medical student. Through my fellowship and my residency, we continued many of these trials, as well as their data collection and clinical monitoring.

The number of FDA trials that I participated in as a primary investigator, associate investigator or peripheral data collector is many. These trials have included pharmaceuticals, techniques, technology and at present laser vision correction. Today at my center we are actively involved in seven different FDA trials. It is with this background that I come to you today to try to present one person's opinion with regard to this data collection set.

I have submitted data, both for the Summit and VISX laser arms in this trial. I have participated in this trial since its inception when roughly 20 surgeons came together and decided that we needed to validate laser assisted in situ keratomileusis. We felt that our techniques and technologies were evolving toward LASIK and the laser manufacturers had no incentive to go and try to get approval for these techniques and technologies. With the brainstorming of several individuals these trials were put together. I applaud their efforts because they have not been easy.

With our support, both physically and financially the data is now being reviewed after 3 years. Some have chosen to criticize the feasibility of a surgeon-funded study. As a participant in many FDA trials, I can assure you that the rigors that I went through with this trial were equal to that of any other FDA trial. These included site visits as well as clinical monitoring and clinical monitoring of the data collection sets.

Although we did not have the economics to promote the fanfare of meetings and publications of our early work, the participants paid to hold regular meetings to present the clinical data in controlled forums. This allowed us to monitor the data and monitor our progress as a group and as

individuals.

An FDA approval of LASIK will improve my delivery of medical care. At present I cannot discuss LASIK with the laser manufacturers. That creates a problem with application of the technology and techniques using the laser that has been approved for photorefractive keratectomy but is used by the majority of the ophthalmic community for laser-assisted in situ keratomileusis. The development of LASIK nomograms are definitely surgeon dependent; however, as with PRK we see that those laser nomograms can be improved when the laser companies and the surgeon are in direct communication. The inability to freely exchange ideas did not originate with the surgeons and the manufacturers. It extends from the restraints imposed by limited approval. Today we have manufacturers making lasers for photorefractive keratectomy that are in fact used for laser-assisted in situ keratomileusis. They should be able to make lasers that are specific for laser-assisted in situ keratomileusis. The difference may not be major but there will be some differences in the computer software programs for the use of these lasers with regard to specific patients and patient treatments.

Although clinical trials have never been a problem to me, they are foreign to many individuals in the general

ophthalmic community. I think using a device as an off label is the choice of the surgeon, but it would be better if we had the process approved so that discussions among the laser manufacturers and surgeons could take place.

At present my patient population is confused as to what we are really doing. Why are we performing LASIK when the FDA has labeled the lasers for PRK? I do not think that sends a good message to the general population. The informed patient is a better candidate. At present when I advertise laser-assisted in situ keratomileusis I do it as a clinical treatment trial. There is always an asterisk that labels the FDA protocols we are going through. I know it is a better procedure. I have done both PRK and LASIK, but PRK has the official standing of FDA labeling. It would be much better to send a consistent message to the patient population as a whole.

I understand that there are no good guys and no bad guys in this equation. As I understand it this is the first collaborative LASIK trial to come before this Panel. My point is not to lay blame but to encourage a remedy for the current situation. As a profession we simply must bring the labeling in line with the actual use of the lasers.

There will always be new technology, and there will always be FDA treatment trials for new technology.

Through the efforts of the CRS LASIK study, laser-assisted in situ keratomileusis now has a proven track record. Yes, there is room for LASIK to improve. Much of the data in the CRS database were early cases done by pioneers in the field while trying to iron out nomograms and techniques. Yet, the data is good. LASIK is a proven procedure.

I see a bright future for physician sponsored studies. When industry and physicians can work hand in hand, it makes it much easier for those involved as well as it produces better outcomes for patients. Our profession has a history of constantly striving for better techniques and technology. I think that industry cannot always afford to burden the load of clinical studies and the approval process. I applaud those individuals including myself, for contributing the effort and money to bring this study to this point. I challenge the critics to look at the data in the clinical setting and the clinical monitoring in a true light.

The CRS LASIK study has been conducted as a true clinical treatment trial. I consider the protocols and follow-up equal to any other FDA study that I run presently. I treat patients in this study no differently than any of my other trials and rely on the clinical monitoring in the same fashion as any of my other industry-related FDA trials.

There may not be as many bells and whistles in this study, but it has been efficiently run. I applaud those individuals who have put this together and who have persevered through the trials and tribulations associated with the start-up process like this one.

I want to thank the Panel for giving me the opportunity to make these comments. I intend to be here all day if you have any additional questions.

Thank you.

DR. MC CULLEY: Thank you.

Do any of the members of the Panel have a question for Dr. Stonecipher?

Seeing none, Dr. Arrowsmith?

Thank you, Dr. Stonecipher.

DR. ARROWSMITH: Good morning. My name is Dr. Peter Arrowsmith.

DR. MC CULLEY: Please state any conflicts or support or anything or lack thereof?

DR. ARROWSMITH: I have no conflicts of interest and no financial interests in any of the companies involved or products involved with LASIK. I am a board-certified ophthalmologist, licensed and practicing in Nashville, Tennessee, for 22 years. I am an active member of the American Academy of Ophthalmology, the American Society of

Cataract and Refractive Surgery and the International Society of Refractive Surgery, as well as my own state and local societies.

I wish to speak to you this morning as an experienced refractive surgeon who has, also conducted research in this field for approximately 2 decades, first on my own and then with a group of four researchers with two very experiences academic researchers and now with the CRS study group. I wish to share my opinion with you of the CRS study.

Since 1980, my practice has predominantly focused on refractive surgery. I have performed a wide variety of procedures including approximately 5000 RKs, 00 Barraquer Cryolathe Keratomileusis procedures, the forerunner of RK, ALK, PRK and now over 2000 LASIK procedures. I, also perform intracorneal ring implantation and Artisan myopic lens implantation. I have authored and published a number of scientific reports, reporting results of my prospective studies of RK including 5-year results and a mathematical prediction model for that surgery.

I have been invited to present my work at the National Eye Institute and have been awarded grant approval for two prospective refractive surgery studies. I have, also been a consultant to the FDA PERK study for RK. My

practice is now devoted exclusively to refractive surgery and related research. I care a great deal about refractive surgery and the care and results provided for patients of my own and this country's increasing number of refractive surgeons and their patients.

When I began performing LASIK approximately 3 years ago, after a number of PRK procedures I quite naturally wanted to follow my results with the primary goal of constant monitoring of results, improvement of my technique and improvement in predictability of this procedure which was as I found so much better than its grandfather Cryolathe keratomileusis a decade earlier. I began this study on my own but soon became aware that the CRS study group was undertaking such a study, and I might be able to participate in this. Upon investigating the CRS study, including its protocol, its training requirements, not only for the surgeon, but, also for the office staff, to ensure reliable data collection and reporting the scale of the study and its scope and importantly its key directors, Dr. Charles Casebeer and Dr. Guy Kezirian I became convinced that this was a study that I wanted to be a part of.

I felt that in this study I could make use of a well-organized and scientifically sound protocol. I could then receive help from the directors and their staff in

monitoring the data entered by my office in terms of quality and completeness, obviously crucial to being able to retrieve any useful information upon analysis. I could, also, receive assistance with the analysis from qualified and experienced researchers who understand ophthalmic data and I could participate in the sharing of results, experience and brainstorming with like-minded colleagues at frequent meetings of study participants, and I must note that at these meetings they, also, served to promote the scientific purpose of the study and continually encouraged completeness and best possible follow-up and to answer questions and provide guidance on issues of study administration within our individual studies and practices.

I am pleased to say that my expectations for the CRS study most definitely have been surpassed. Participation in such studies is not without a price. I devote resources to help support the CRS study. This includes fees paid directly to the study and the cost of extra staff and their man hours required in the practical administration of the study in my practice.

The CRS study has demonstrated that LASIK performed as prescribed upon eyes of qualified patients using the VISX Star and Summit Apex laser with the Chiron Automated Shaper or the Chiron Hansatome is a safe and

effective refractive procedure. This conclusion is clear based on the CRS data study quality and on the findings of the study which meet or surpass the FDA's specific criteria for unaided visual acuity, change in best-corrected acuity, refractive results and adverse effects.

I am still an investigator in three CRS FDA studies for hyperopia and its subgroups. In addition, I am a Phase II investigator in the manufacturer's FDA study of the Ophtec Artisan lens for correction of myopia. So, I will be continuing to learn from all of this work. I am pleased and proud to be a part of this CRS study. I made the right decision to participate in this scientific study group and its very worthwhile efforts towards studying and elucidating the results of a treatment modality which is used by the vast majority of laser vision correction surgeons in the United States in preference to the initially approved PRK.

This is because it has been found to be better patient care and although participation in such studies is not without a price, these are resources well spent when spent within the CRS study. It is a study of excellent quality. Its findings speak for themselves. Please give the CRS study and its findings, as well as its request for a PMA your most favorable review. It deserves this on all

counts as do the surgeons who perform LASIK and the patients who benefit from this advanced technology.

Thank you.

DR. MC CULLEY: Thank you, Dr. Arrowsmith.

Do any of the members of the Panel have a question for Dr. Arrowsmith?

Seeing none, Dr. Liang?

DR. LIANG: I am Dr. Keith Liang. I was previously on the Advisory Panel for LDC. I am no longer on the Advisory Panel, and I have no other conflicts of interest.

Good morning. It is a pleasure to be here. I want to echo my sentiments with the previous two speakers. Intraocular implants, clear corneal cataract surgery, macular pucker membrane peels, trabeculectomy and minomicin(?) an LASIK, all these advances in our field by innovative, thinking physicians, as physicians we are encouraged to think outside the box in order to continue advancement in our field of ophthalmology. The ability to solve problems, create solutions attracted many of us into medicine. The challenge to invent new instruments, refine surgical techniques, design new drugs provides an ongoing stimulation in our careers and our lives.

It is this innovative thinking that benefits our

patients' vision, and this continued innovation led me to explore LASIK as a better alternative for my patients. The ability to make a difference attracted me to join the clinical study for LASIK. As a resident at LSU, we were one of the original Taunton(?) and VISX sites taught me the value of research by clinical trial.

The firsthand experience allowed me to appreciate the effort, determination and time required to bring a good idea to clinical application. During the involved process it became evident that a variation of the original PRK protocol could be beneficial or more beneficial to our patients. When at 2 am in the morning I have to call in Demerol shots for PRK patients, control their high pressures from post-op steroid regimens and also explain corneal haze to higher corrective myos, I realize that better alternatives must exist. I began to hear and explore alternatives from my international colleagues called LASIK which alleviated many of the patients' undesirable effects such as pain, slow visual recovery and haze from higher corrections.

I realized the effort to bring this innovative idea to the US would be in the best interests of the patients. After observing the procedure firsthand in 1995, and examining the patients I realized this would be an effort that I wanted to put forth in helping bring this

technique to the United States.

The CRS study for LASIK continues this innovative thinking and allows physicians to regain some autonomy in the direction of refractive surgery. It enabled us to study a procedure which we felt was best for our patients and allowed us to validate what we felt clinically. The study allowed for an efficient enrollment of patients in a timely fashion. The study protocol and the reporting of information allowed quick and easy review to allow feedback to the investigators in a continuing fashion.

The Panel's expedited review of the CRS data and possible approval encourages us that we can still make a significant difference and a contribution to the current health care system, that our continued innovations will benefit the advancement of our surgical specialty and the benefit of our patients.

Thank you.

DR. MC CULLEY: Thank you, Dr. Liang.

Do any of the Panel members have questions for Dr. Liang?

Seeing none, we now have a few minutes remaining in our 30-minute open hearing discussion. One individual did call in and make a request. I, therefore, will give that individual precedence. Anyone else, time allowing, we will

allow further comments. The time restrictions will continue on individual speakers, and I would now like to offer Dr. Ron Link the opportunity to speak.

PARTICIPANT: You put an MD after his name.

DR. MC CULLEY: Mister, sorry.

MR. LINK: For clarification purposes, yes, I am a consumer, not a doctor.

DR. MC CULLEY: Thank you. I was going to say either that or you are British, and if you will state any interests, conflicts that you might have, financial interests?

MR. LINK: I have no financial or other conflicts with any proceedings here today.

DR. MC CULLEY: And you paid your own way here and home?

MR. LINK: Absolutely. Good morning, members of the Ophthalmic Devices Panel and members of the audience. I am thankful to be here today. I am here as a representative of the Surgical Eyes Foundation, a grassroots organization formed by consumers whose eyesight was needlessly damaged by the refractive surgical procedures of ALK, RK, PRK and now, LASIK. Our goals are simply these, to raise awareness of the issues, identify lasting solutions and provide support for the post-refractive surgical failure. It is our

committed stance to work with the industry, not against it.

The phone book version of our web site rests here under my hand. Our web site in its current form just had its 50,000th visitor since its inception just over 2 months ago. During this period I have answered over 1250 e-mails, a significant percentage from people who have had negative outcomes from LASIK.

There are some of you here today who may be thinking, of course, there are going to be negative outcomes. No surgical procedure is without risk. We agree. We are here to work in concert with the medical community and I say, again, not against it. That being said we are compelled to call attention to the hard-earned larger truths that we, the casualties of refractive surgery have learned and will have to live with for the rest of our lives.

The standard of care in refractive surgery must be raised. How? In two fundamental ways. No. 1, using new modalities to determine what qualifies as a successful outcome, meaning in clear English that potentially debilitating complications be defined to include ghosting, polyopia, starbursts, glare, haze, blur, halos and any other symptoms currently not acknowledged in contemporary and historical complication rates.

You will most probably hear talk today of BCVA,

best corrective visual acuity. The ability to recognize symbols of our language in the controlled static high-contrast environment of a doctor's office, letters of the alphabet on an eye chart, a device invented in 1862. The time is now to include other modalities besides an eye chart invented more than a century ago as a primary indicator of post-refractive surgical success as represented to the public through print, radio and other media.

No. 2, better pre-op evaluation, namely, identifying counter indications to surgery meaning sharing with the patient how the consent form applies to their own unique set of eyes and expectations, measuring pupil size, contrast sensitivity testing before and after, glare testing before and after, testing for predisposition to vitreous detachment, keeping up with all the latest scientific journal literature, identifying pre-existing ocular conditions like eye muscle imbalances which might be exacerbated, warning the high myo that the chance for complication is greater. Thirty-five cents from every contact lens sold goes into R&D, research and development. There ought to be a fund set up which comes out of refractive surgery profits to study and develop lasting solutions for the post-refractive surgical failure.

Many of the hundreds of negative outcomes which

have e-mailed our web site were, in fact, preventable had there been an aggressive mechanism for identifying and sharing all complications. Given the proliferative success of current procedures like LASIK is there even less of an industry inclination to study and acknowledge poor outcomes? If there is substantive help, why are hundreds of failures in the just 2 short months of our existence ending up at our web site? We are just ordinary people. Clearly something is wrong.

Why isn't there a national industry or surgeon association maintained database of agreed-upon complications that include those crowding at our door? Is it the responsibility of the patient to have to form and join an organization like ours? If the post-refractive failure only tells their surgeon, and that is as far as it goes, how can anyone say that they have accurate complication rate figures? Of the stats that have been maintained by different laser centers complication rates vary from zero to 15 percent and there is the lack of agreement on what qualifies as a complication.

Quoting the doctor who spoke here previously if the data is good, the data is not complete. As a former career firefighter I used to drive a hook and ladder and put up 100 foot aerial ladder during a late night thunderstorm

within inches of a peak of a roof where men's lives depended on it. Today because of my refractive surgery I cannot even parallel park a small Toyota once the sun goes down. Since my surgery I see five traffic lights instead of one, and oncoming traffic looks like an approaching phalanx of exploding stars. My eyesight is a success according to techniques promulgated by a manual taught to thousands of surgeons from coast to coast. I am defined a success. Despite the published scientific journal of Drs. Applegate and Holiday who clearly warned in published results years before and after my specific surgery that pupil size was of critical importance, there was no mention of pupil size by Dr. Case Baird, the author of the manual on which the parameters of my surgery were based.

For the sake of the future of LASIK and the welfare of patients who have the right and the expectation of good eyesight I hope and pray that what is offered here today will indeed raise the bar for the standard of care as it applies to LASIK. We strongly encourage the FDA and all ophthalmic professionals to do what is necessary to prevent the recent and present history of refractive surgery from becoming the thalidomide of tomorrow.

In this bag, all the contact lenses, devices and drops that I have tried since my surgically created visual

deficits. Members of the Panel and audience, thank you for your time.

Mitch Farrow who is a member of our board of trustees is, also, here, and if there is an opportunity would like to speak for just a few minutes.

Thank you.

DR. MC CULLEY: Thank you, Mr. Link.

Are there any questions of Panel members for Mr. Link?

Dr. Bullimore?

DR. BULLIMORE: Thank you for your comments. Just for clarification, which procedure did you have?

MR. LINK: I had radial keratotomy April 7, 1995.

DR. BULLIMORE: Thank you.

MR. LINK: I have copies which go into further detailed, culled from our web site which I will leave on the table outside.

Thank you very much.

DR. MC CULLEY: Thank you, Mr. Link.

We are nearing very closely the end of the 30-minute open session.

Are there any other people in the audience who would like to speak very briefly?

Okay, you have, can you do this in 2 minutes?

MR. FARROW: I will try my best.

DR. MC CULLEY: That is what you have.

MR. FARROW: My name is Mitch Farrow. I thank the Panel for the opportunity to speak today. I, also, do not have any conflict of interest or any financial interest in laser vision correction. I am, also, representing a consumer of LASIK. When I drive to work every day, fighting the DC traffic I hear lots of great advertisements including the advertisements from the center that did my surgery talking about 95, 98 percent, whatever the percentage is of their patients who achieve 20/20 or 20/40 or better vision, and they consider that a success. I am considered a success by that criteria as well.

However, in anything but extremely bright daylight I am visually impaired by starbursts, halos, multiple ghost images because of LASIK done on my 8-millimeter pupils. I am not asking you today to not approve these devices or to not advance refractive surgery. In fact, I want to see advancements so that they can improve my conditions. What I am asking you today is to consider all the issues with respect to visual quality in assessing these devices. Specifically I ask the FDA to consider the following: No. 1, expansion of required clinical trials, study parameters to include contrast sensitivity testing, both pre- and post-

op, glare testing, pre- and post-op, incidence of diplopia and third-party independent assessment of vision.

When I go to my surgeon and they refract, do testing on me, they test me at 20/20. When I go to other third-party independent objective medical professionals they test me at 20/30, and they do refract me as well. No. 2 is FDA approval of devices should include not only approval within a certain range of myopia or astigmatism or hyperopia but within a range of pupil sizes such that any use of that device outside of that pupil size should be considered against the FDA approval of that device, and finally, and I am trying to make this short because I have 2 minutes, third of all, the FDA should create and enforce guidelines regarding advertising and marketing of these devices. I do see a guideline here that was included in the packet. I found out about this meeting last night, went home, opened my Newsweek, and there is an ad for, I guess Crylosak(?) with about a paragraph of benefits, a couple of paragraphs of side effects, an entire page of warnings and indications. There is an ad here for ZOFOR(?) again with a couple of paragraphs of complications, side effects, an entire page of contraindications and side effects, and finally, an advertisement for laser vision correction with a paragraph of how this is doing to improve your visual acuity, you

know, great things and no indications of any potential side effects. If I read your guidelines here, the marketing of RKPRK LASIK to consumers should not contain express or implied claims that are false or unsubstantiated or omissions of material information. I think my inability to see in the lighting in this conference room is an omission of material information, and I respectfully submit that to you today.

DR. MC CULLEY: Thank you. Are there questions from the Panel members?

Seeing none, we thank you, and this concludes the open public hearing. We will now begin the open committee discussion with Dr. Rosenthal giving a division update.

DR. ROSENTHAL: Thank you, Mr. Chairman.

I will take the opportunity to thank the Panel for coming and knowing that they have 2 rather arduous days and four applications, and we very much appreciate all the effort that they put in as primary reviewers and all the advice that they will be giving us.

I have some news about personnel to the Division of Ophthalmic Devices. We have added four members, three who are on board and one who is coming on board next week, Joel Glover who is a biomedical engineer who has arrived from the NIH, the National Eye Institute, with a long

history of ophthalmic research behind him, Eva Rohrer who is a medical officer who has just finished her fellowship at Johns Hopkins, Eric Selfontz who has arrived to do some of the technical administrative work and is a CST. I never can remember what it means, but consumer safety technician, and Karen Copeland who will be a secretary who will be joining us on August 1.

I should like to, also, inform the Panel that the Division of Ophthalmic Devices has been enlarged by an additional branch called the Ear, Nose and Throat Branch and one day we will rename the Division which will appropriately designate that ear, nose and throat is, also, part of the Division of Ophthalmic Devices, but we will not ask this Panel, probably to rule on EMT devices in the future.

I, also, would like to make a statement concerning bioresearch monitoring. I think when most of the Panel members are indoctrinated into the system they are given some information about bioresearch monitoring, but many of the new members may not know what it really is and many of the members of the Panel who have been around for a while may have forgotten. So, I would like to refresh your memory in a generic way.

The Food and Drug Administration's bioresearch

monitoring program or BIMO was established in 1977 by a task force that included representatives from all the FDA Centers. Congress mandated that FDA develop and implement an agency-wide program. BIMO monitors sponsors, IRBs, clinical investigators and non-clinical laboratories involved in the testing of investigational devices.

The objectives of BIOMO are twofold: One, to ensure the quality and integrity of data and information submitted in support of an investigational device exemption, and IDE, premarket approval applications, PMA, and premarket notifications (510(k)s); and two, to ensure that human subjects taking part in investigations are protected from undue hazard or risk.

The Division of Bioresearch Monitoring's operations are directed toward several program areas. These include: (1) audit of clinical data contained in PMAs prior to approval; (2) data audits of IDEs or 510(k) submissions; (3) inspections of non-clinical laboratories that perform medical device related safety testing for inspection of IRBs that monitor investigational device studies; (5) enforcement of the prohibition providing education, training and guidance to regulated industry and (6) implementation of FDA's Application Integrity Policy.

If you would like additional information about

bioresearch monitoring, please contact Charma Konnor who is the Director in the Division of Bioresearch Monitoring. That applies to all PMAs.

Another item I would like to bring to the attention of the Panel concerns some of the complaints we have received about the sunrise PMA which we will consider this afternoon. FDA and Panel members received several complaints that Sunrise's clinical investigators held significant amounts of stocks, options or warrants in the company and that by virtue of these equity positions the data generated by these investigators was, therefore, biased.

One of the faxes contains complaints about the design and execution of the study as well as the question of bias in the study. The issues raised by these complaints are not on the agenda for Panel consideration. FDA advisory panels were established to advise the agency on scientific and clinical issues that arise during the consideration of applications and other clinically related issues. They are not intended to deal with conflict of interest or data integrity issues.

If we find that data in an application suffers from such infirmities that application may not be presented to the Panel until all such issues have been resolved

satisfactorily. In fact, when issues related to the integrity of the data are discovered appropriate action may be taken at any time prior to or after Panel review or at any time prior to or after FDA approval of the application.

FDA is concerned about the integrity of the data or the design and conduct of the studies in all of our applications, and we have a very active and effective program to assure our decision making is based on accurate, complete and unbiased data and information.

Our staff takes very seriously any allegations concerning these matters, and we will look into these allegations and take whatever actions are appropriate. However, our investigations are discussed in camera and not discussed with the public or with the informants from whom we have received information.

Thank you, Mr. Chairman.

DR. MC CULLEY: Thank you, Dr. Rosenthal.

We will now begin deliberation on PMA P990010. We will begin with a 60-minute sponsor presentation, and again if each person who speaks for the first time will identify yourself and your position relative to the PMA?

DR. KEZIRIAN: Good morning, ladies and gentlemen. Thank you very much for allowing me to appear before you and thanks to the FDA staff for a lot of cooperation and

courtesy during this. I am Charles Casebeer. I am Chairman and founder of CRS Clinical Research, the applicant for this PMA. I am the senior medical monitor of the CRS LASIK studies and so you know I have no financial interest in any of the products that are involved, I guess, other than the fact that I am the Chairman of the company that is sponsoring the PMA.

I thought it might interest you to know a little bit about CRS before we really get into it. So, we are going to present you with this agenda, the goals of the study, the history and evolution of CRS and this study done by myself, then the study logistics, monitoring and results by Dr. Guy Kezirian and then a few concluding comments at the end by myself.

CRS started in March 1996 to look at what was going on with LASIK when we became aware that although the laser had been approved for PRK, it seemed and it turned out to be true that the majority use was going to be in LASIK, and it brought up some issues about the public welfare, performance of the lasers in a procedure that had not really been studied before. So, we formed this small group, at that time totally independent of anybody with the surgeon-funded study before it became an IDE to study this procedure.

We formed an affiliation with the International

Society of Refractive Surgery and our goal really was to try to validate or invalidate for that matter the use of the lasers in LASIK.

In the summer of 1996, we had a meeting with the FDA, and it was requested that we convert this to a federal IDE which we have done. The letter of approval was received in October. There is an explicit letter of understanding about how it will be performed and frankly at that time we didn't know or even expect that we might have the opportunity to submit or participate in the submission of a PMA, and we are very grateful to have that opportunity.

What we wanted was for the American ophthalmologists, the people in the trenches who have a lot of skill and interest to participate in the validation and refinement of this procedure and based on early experience we knew that we needed to study the application of the PRK algorithm to LASIK.

Mostly what we wanted was to make the procedure safe for the public and discourage unproven application of laser technology beyond the limits that were known to be valid. So, what we really hope that this will lead to is validation or approval of LASIK with the technology that is available in America today through the normal FDA approval policy and that it will be for all doctors and all of the

public rather than for a few doctors or a small sector of the public, and we have given a lot of interest in software-specific matters for LASIK and of course, we hope that labeling now will allow the technology to be LASIK specific.

We set the study up, and Dr. Kezirian will tell you much more about it to be practical, to be compatible with the practice of ordinary practitioners. He will tell you that we taught them how to be clinical investigators but we did not want it to be onerous, and of course, we obviously wanted to study standards of care and affect standard of care, make nomogram adjustments and ultimately as we are with this application establish performance criteria for higher myopia and allow which we have been this interactivity between ourselves and the investigators to become aware of things that either are problematic or that might improve the safety and effectiveness of the procedure.

This application involves a combination of two CRS studies, one LASIK and the range for which the lasers are approved for PRK and then what we designated substudy A which includes high myopia and astigmatism. Our company has multiple other variations with both VISX and the Summit laser relating to hyperopia and other variations of that, and we are conducting a similar study on behalf of the Nidek laser.

The study has been open to qualified ophthalmologists. The qualifications are clear but we do hope that it is a reflection, and we think it is a reflection of LASIK in general use as opposed to smaller areas, research centers, companies or other things. We do have IRB oversight and of course, we do conduct it as an IDE.

So, I am very grateful to be here with you, and I will introduce Dr. Guy Kezirian.

DR. KEZIRIAN: Good morning, and thank you for this opportunity to present to you this morning. I am Guy Kezirian. I am a consultant to CRS. I have been from the beginning of the study and work for CRS in a capacity as such. I have been involved with the study from the point of view of helping to write the protocols, liaison with FDA, helping to recruit investigators, organizing the meetings, personally crunching the data, the database involved with that, personally, with assistance preparing the applications. So, I have a thorough exposure to the study from its beginning to today.

The data collection process was one of the things that empowered the study to actually work. We had a program called data site which allowed for remote data entry at each clinic directly in and avoided a whole layer of paperwork

and a whole layer of logistics for us and allowed us to impose these things called data entry filters which are simply range filters on the data to prevent 100 being put in for 10, for example. What it didn't do, what these data filters don't do is to take two plausible entries and know that one of them is wrong, for example, saying that a patient is a plano(?) and uncorrected acuity of, or let us put it the other way, patients of minus 10 and uncorrected acuity of 20/20. It didn't have that ability to do those relational things.

So, those problems that did exist, dates being juxtaposed, that sort of thing that weren't caught were hand picked out through a systematic way that we developed and have been listed in the application for your perusal.

But overall that program was very, very helpful to us in limiting data entries and allowing us to accumulate a rather large database in a rather quick fashion.

We were very careful to have the sites conduct the study in a uniform fashion and to do that took a certain amount of time, but Dr. Casebeer and/or myself visited every single site as it got going and spent time educating and presenting to the staff and the surgeon about study conduct, requirements for logistics and compliance and exactly what we expected of them.

We performed ongoing data monitoring for reporting compliance, adverse events, nomogram development and other things that will come up a little bit later in the presentation and that occurred on a continuous basis, and we presented those results three to four times a year in public to our presenters, to our investigators and to the affiliate society, ASRS. So, we obtained a large amount of feedback as we progressed with the study.

The studies inclusion criteria have been listed in your handout, and they are for bilateral pre-existing, naturally existing spheroequivalent myopia of minus 1 to minus 15 diopters with .25 to 6 diopters of astigmatism in a stable eye. Gas permeable contact lenses were required to be out for 3 weeks and soft lenses for 3 days, 18 years or older or enrollment and signing an informed consent and able to complete the 6-month follow-up.

The exclusion criteria are listed here in summary. The eyes were required to be normal, no previous surgery, diseases. The last item, diagnosed autoimmune disease as an exclusion criteria is something that I believe will come up in the FDA's comments. We were able to exclude patients on medication, system medications for autoimmune disease by excluding the disease per se.

Operative parameters with the VISX STAR laser were

an ablation zone of 6 millimeters, confluence of 160 milliJoules per centimeter squared, repetition rates of either 5 or 6 Hertz. One keratome was used in this entire study which is the Chiron ACS. We currently are using other keratomes, but the data were cut off at such a time that those keratomes hadn't yet been introduced. So, your data are pure with the Chiron ACS keratome, and the calculations pre-operatively were required to predict at least 250 microns residual corneal tissue to remain after the ablation.

Nomograms were used and encouraged. We found very early on that the difference between the PRK and LASIK algorithms with the VISX STAR laser are significant, and in fact we suspect that our ability to recognize through collaborative databasing and our ability to publicize that as we did may have saved the overcorrection of many eyes around the country.

Nomograms were developed in conjunction with CRS. We would actually participate and actually crunch the numbers for them and help them to understand what nomogram adjustment to make to their particular procedures based on their own outcomes. Fellow eye treatments were permitted same day if everything went well in the first eye, but if it didn't then not until the first eye had been recovered to

best corrected acuity of the pre-operative level and then it would be permitted at that point.

Reoperations were allowed but only after 3 months which allows us to present to you in a 3-month time period only single procedure outcomes, and as you will see they are quite strong and speak for the single procedure success of LASIK but by no means suggest that second procedures aren't a part of LASIK because they clearly are in some eyes.

We froze the protocol for June 1, 1998, to allow us to present to you completed patients from the study. Follow-up was required at 1 day, 3 months and 6 months. A 1-month exam was optional but was provided from many centers to allow us to accumulate stability. Investigators consisted of 11 surgeons at 11 centers and overall there were 1276 eyes submitted in the PMA application, in the overall cohort. We chose to divide the cohort into two subgroups, what we termed the PMA cohort where we took the data from any investigator whose compliance was 80 percent or better at the 3-month observation and we had in that group 723 eyes and 11 investigators that were used for the safety and efficacy evaluation. That allows us to satisfy good accountability at 3 months and have reliability on the efficacy rates.

The remainder cohort was the rest of the

investigators whose 3-month compliance level did not meet 80 percent. These were, also, submitted in the PMA and used to verify safety. We had eight investigators and 553 eyes in that group. We examined them rigorously as requested by FDA in several different ways for differences between the two groups and found no statistical differences between the two cohorts, with the exception of a slight trend, not statistically significant for the remainder cohort, the one that was not used for efficacy to have better results, the explanation being that from the investigators anyway that the patients with the good outcomes were difficult to bring back for the 3-and-6-month exams.

Study results. Accountability is shown here with 90.3 percent at 3 months, dropping to 76.3 at 6 months. We had 90.3 percent Caucasian, .7 percent black, 4.9 percent Asian and 4.1 other in a demographic race distribution, a slight preponderance of females to males in enrollment and right and left eye distribution rather symmetric.

The age distribution mirrors the age distribution seen in most refractive study reports, with the preponderance in the middle-age range, a mean age of 41 plus or minus 9 years which is almost exactly what other people seem to report. A range of 18 to 65 years was reported in the study. Attempted corrections averaged 5.85 diopters in

sphere only corrections with a range of 1 to 13.76 diopters. Sphero-cylinders averaged 594, quite close with a range of .25 to 14 and a mean attempted correction of cylinder of 1.19 diopters. Now, these were the attempted corrections, amounts actually attempted to be achieved as opposed to the pre-operative refraction which differed slightly, people sometimes attempting to correct less than the full amount.

These are reported here with a distribution that mirrors somewhat the general population. We have a little bit higher representation in the upper refractive ranges about 20 eyes above 12 diopters a little bit higher representation than you see in the general public which we thought would be good for evaluation in that range.

Pre-operative cylinder distribution focus is mainly up to 3 diopters. Beyond that we have 11 eyes. This actually exceeds the distribution in the general population again. It helps us to evaluate outcomes in that range.

Pre-operative best corrected visual acuity was 20/20 or better in 92 percent of the eyes and worse than 20/20 in 8 percent with the corrections under 7 diopters.

One of the protocol requirements, if you recall was best corrected acuity of 20/40 or better. So no one was worse than 20/40. In the higher group 78 percent were 20/20 and 22 percent fell below 20/20 and better than 20/40. So,

that perhaps impacted our later results a bit.

We present safety results first. The targets that are listed here are the targets that are provided in the October 10, 1996, FDA guidance document. Our actual risk protocol predated that guidance document. We came close on most of the targets and in fact, I was serving on the refractive technology forum at that time and had some ability to try to match them, but what we did with our subsequent protocols is to exactly match them. So, what we are doing today in that request of FDA is to present to you our results against the published guidance documents.

They are listed here, and I am sure you are familiar with them. On the loss of two lines or more best corrected visual acuity the target rate is 5 percent, and in all eyes for either of the refractive subgroups we fell within the 5 percent level, getting up to 1.4 percent in the over 7 diopter group at 3 months but that actually improves at 6 months to .7 percent.

Best corrected visual acuity of worse than 20/40 the target is 1 percent. We meet it for all eyes but exceed it for the over 7 diopter group and we do so slightly both at 3 months and 6 months although with a trend toward improvement. The less than 7 diopter group did not experience this complication, remembering again that some of

those eyes were close to 20/40 when they began.

Best corrected acuity worse than 20/40 in the higher group was a question to us because we were concerned that perhaps it was a trend that the higher you went the more best corrected acuity loss you would achieve. So, we look at it in terms of 1 diopter stratifications and find that in fact it is not a trend. There is this little cluster between 9 and 11 but no trend for loss of best corrected acuity was apparent as you went higher, and remember that the number of eyes although we probably were better than the general population the number of eyes in the higher ranges was very low. So, any given eye has a significant weighting of percentage rates of outcomes. We actually had four eyes at 3 months that met the target of 20/40 or worse and two eyes at 6 months but because of the dwindling Ns toward the higher refractive ranges those two eyes and four eyes end up exceeding the target.

Inducing greater than 2 diopters of cylinder and spherical corrections, in other words causing cylinder where there was none did not occur at all in this protocol either at 3 or 6 months either for low or higher myops, and adverse events occurred with these rates. The black numbers are within the target of 1 percent. Interface epithelium was reported at 1.2 percent rate but we found that we looked at

each of these eyes and none of them were beyond trace, so a little nest, a small nest of cells, none with best corrected visual acuity of 20/25, worse than 20/25 in this group.

So, although that existed and as an absolute on a rating scale, none were worse than trace.

Operative complications, intraoperative complications existed at these rates with some of these being more observations than complications, for example, a free cap isn't understood to occur at its given rate, but there have been reported here in detail overall .1 percent of procedures were aborted because of an intraoperative complication. That was related to a keratome. There were no procedures aborted due to a laser failure, and despite again that list of complications that is up again, surgery did not have to be aborted except for in .1 percent of eyes.

Complications reported at 3 and 6 months are listed here, and because we did not control for dry eyes in the study they had to have a normal ocular exam, we suspect that the staining that is reported here at 2.3 percent may be related somewhat to a dry eyed population but we cannot verify that. It is pure speculation.

Cumulative complications reported, how many eyes experienced any complication at any time point was 4.1 percent, whether in the low or high group, treatment group

and again that similar complication rate was reassuring to us that by going higher we weren't automatically causing more complications.

We did not find a significant ability to predict what would happen to IOP after LASIK. We did find that overall the trend was for the intraocular pressure to decrease. We had a small group of eyes that increased between 1 and 5 points, but we didn't find any eyes that or we didn't find any trend to the pattern of overall IOP reduction. We looked at it from every point of view and tried to regress against everything at FDA's request to try to obtain a formula by which we could predict in the future how much IOP change would occur, but we were unable to do so. However, we did meet the requirement for not having IOP elevations above 10 in this series. So, IOP is not a complication of LASIK in this area which is a significant benefit in my mind.

To summarize the efficacy results again using the FDA targets listed here, you will see that we actually add an extra slide because it often comes up what was the 20/20 rate. So, we provide that information as well, but it is not a stated FDA target in the guidance.

We showed using the mean measurement method to evaluate stability the mean spheroequivalent in a paired eye

analysis, you understanding that a paired eye analysis is to use the same eyes for measurement at each interval as opposed to whoever shows up for one interval against whoever shows up for the other interval to allow you to have tracking of patient-to-patient what happened in those eyes. This is a paired eye analysis and in all eyes we show very little change in the mean sphere of equivalent from 1 to 6 months, the same in the 7 diopter or less range and the same in the 7 diopter to 14 range with less than .2 diopter drift in the mean spheroequivalent. However, if you look at it in the other way of looking at stability how many eyes showed less than 1 diopter spheroequivalent change in two observations we show with a target rate of having 95 percent of the population showing less than 1 diopter change, we show that for all eyes we almost make it at 94 percent. We do exceed it at 96 percent in the under 7 diopter group, and we fall short in the over 7 diopter group at 3 months, 1 to 3 months. Going 3 to 6 months we meet it in all eyes. We meet it in the under 7 diopter group again, and we still fall short in the over 7 diopter range.

So we show that the mean change in the population was minimal after 1 month. Stability was achieved beyond 3 months per the FDA definition for the overall cohort and beyond 1 month for the less than 7 diopter group, but the

rates of stability were slightly less and took longer to occur in the over 7 diopter group, and we were, also, able to show that there was no difference in stability occurring whether it was a spherical or a spherocylindrical correction.

The target of uncorrected acuity 20/40 or better, the target is 85 percent. We meet that target in all eyes in under 7. We are a little short in the over 7 diopter group at 3 months. We meet it across the board by 6 months with 86 percent in the greater than 7 diopter group and 95 percent overall.

Uncorrected acuity of 20/20 or better, of course taking out the eyes who didn't have 20/20 or better pre-operative best corrected acuity, so you weren't asking an eye that was best corrected 20/40 to see 20/20, looking just at those eyes we find that the 20/20 rates were 53 percent overall and 59 percent in the under 7 diopter range and 39 percent over 7 diopter range, improving a little bit in the under 7 diopter group between 3 and 6 months but staying fairly stable in the over 7 diopter range of 39 percent.

One day visual acuity probably accounts for a great deal of the public's acceptance of this procedure and their enthusiasm for it, and we show why here. One-day acuity of 20/20 is 43 percent in the under 7 diopter group

and 20/40 or better in the under 7 diopter group is 92 percent and that is quite remarkable and allows people to return to functional vision quite rapidly. Even in the high myops it is 72 percent in the 20/40 level on the first postoperative day and clearly presents a relief for the practitioner and the patient alike coming from previous procedures.

The plus or minus 1/2 diopter target is 50 percent. It was met across the board at 3 and 6 months with the rates reported here.

The plus or minus 1 diopter target is 75 percent and it is reported again with everybody except for the over 7 diopter group at 3 months.

Nomograms were used and encouraged in this study and I think are essential in LASIK. We developed them in a process that allowed us to look at the overall laser behavior over the full range of refractive correction. We would create that profile, take an individual's outcomes, compare them to that profile and mean adjust the entire profile to the investigator's outcomes. It allowed us to generate a nomogram with maybe 20 eyes from an investigator but based on thousands of eyes from everyone pooled together looking at the overall behavior of the laser and we were able to monitor how those were occurring and control them

because they reported to us what they were doing in each operative report.

You can see how necessary they were when you look at the no-nomogram-adjusted results when I take the amount that was programmed into the laser versus the amount achieved, a mean of 11 percent extra correction compared to what was expected, and if you look at the plus or minus 1 diopter line which is depicted here, you can see that a significant trend especially toward higher correction of overcorrection that would have been unacceptable.

Nomogram-adjusted outcomes eliminated that tendency for overcorrection. You can see that our regression line falls toward the minus 1, in the plus or minus 1 range, and that was intentional. We wanted to avoid overcorrections. This protocol existed before we had access to hyperopic corrections to come back if you wanted to, and we felt that it was better to leave people under corrected with a second treatment possibility than to all them to be overcorrected and untreatable, and you can see how effective it was in avoiding overcorrections. The trends for spheres and spherocylinders reports are just taken out of these and they exactly mirror these trends. There wasn't any significant difference in those two groups.

To summarize we found significant differences

between PRK and LASIK treatment algorithms about 11 percent on average with a range that went far beyond. It was revealed by our ongoing data monitoring, and we provided constant feedback and were able to impact significantly the outcomes that we achieved by doing so, and it allowed us to obtain more accurate treatment. It demonstrates, I think this was a vivid demonstration of how important it is that software can be adjusted by the user and that individual nomogram adjustments can be made for any laser that is used for LASIK.

This group heard a discussion 6 or 8 months ago about what is the best way for us to look at cylinder outcomes, and this has been a topic that has gone around for a long time. The one thing I heard from that meeting was the SIRC-to-ERC ratio, the surgically induced refractive change, how much you achieved versus the intended refractive change, what you were attempting to achieve, that ration of what did we want versus what did we obtain, provided a nice summary of how much correction the laser was delivering for what it was asked to do, and we present that ratio here on a percentage basis as it is requested in the FDA format, and we show that the ratio was very close to 100 percent across the board. The standard deviation line is presented. The confidence intervals I should mention for all of the things

that we are reporting, stability or these or any of the others are extremely small, .1 diopter range or less because of the large numbers in the study which was helpful to us. Rather than report those which don't show up on the graph, I am reporting standard deviation numbers which provide us with a little more information.

You can see that in the low corrections, the very low corrections, less than 1 diopter the small denominator, half a diopter attempted, achieved a 1 diopter. You have 100 percent overcorrection. So, the standard deviation tends to be heightened by the small denominator in the low group, and it gradually tapers off as you go higher, and you can see that across the board the accuracy was quite good.

The stability of the cylinder correction coming again out of the FDA guidance was very good at 99 percent, the definition of 1 diopter of change between the two observation intervals, and we had that in 99 percent of the eyes across the board.

We did perform a patient subjective questionnaire and say what you will about our ability to measure contrast sensitivity and our ability to measure glare and nighttime complaints, patient questionnaires provide us with a very powerful tool to measure these outcomes and the actual performance in visual function of a patient. We found them

very valuable, and we learned a great deal of information about LASIK.

We administered pre-operatively and at 3 months so that we obtained two snapshots in time. How are you doing with your visual function before the procedure, and how are you doing at 3 months, and for symptomatic questions related to glare and halo responses improved after LASIK compared with the pre-operative level.

We are reporting them here in a little bit different format than I have seen, but it is familiar to you in the sense that the same way we report best corrected visual acuity we take a paired analysis. So, we take an eye and if it improved it goes to the right, and if it worsened it went to the left. So, we looked at the scores, and we said with glare the question was how much glare do you experience in your daily activity, and the patients that reported better were over here, and the patients that reported worse were over here. You see a fairly gaussian distribution which is great news compared to some of our previous procedures which would certainly have gone the other way. We had a mean pre-op of 3.4 and a mean postop of 3.0 and a very significant although not clinically a big number changing 1/2 point on average statistically very significant improvement on the amount of glare that was

experienced. So, if anything in our population we found that glare improved after LASIK.

The story with halos was less dramatic. We had more of a scatter and more of a smattering of responses. We had very similar pre- and postoperative mean outcomes and we did not have a significant difference pre- and postoperatively. That is not bad news. They didn't get worse when compared to their pre-operative appliances to postoperative LASIK, but clearly one of the frontiers in LASIK is to actually try to improve quality of vision than what people were able to achieve beforehand, and we aren't there yet with that.

Vision fluctuation, again, was not a significant change. A higher score is better with vision fluctuation but we didn't show that to a significant level to occur. So, in summary the first, the glare improved. The other two didn't change statistically and we weren't making them worse on our patient subjective questionnaires which was a very, very positive note for LASIK compared to what we have been doing in the past.

We feel, and we encountered reoperations are a significant part of LASIK. We report the rates here based on pre-operative refraction, what the likelihood was to go on to reoperation. It is nearly a 1.0 correlation at .98.

It is clearly related to, the reoperation rate is clearly related to your pre-operative refraction. We did not find it to depend on whether or not you underwent a sphere or a spherocylindrical correction. So, cylinder correction didn't increase your likelihood of reoperation, and we were pleased to see that if we looked at the best visual acuity and the worst visual acuity and they were basically the same, 11 percent lost one line, 11 percent gained some lines. Seventy-eight percent didn't change, and that was I think a very heartening testimony for the safety of performing a reoperation in LASIK.

I have heard an anecdote where LASIK may be the only operation where the reoperation is safer than the original operation, and it could be that because you are not using the keratome, but we sure report here that the loss of visual acuity was not pronounced with patients undergoing the reoperation.

We did show a clear trend toward improving the visual outcome. We went up to, 98 percent of the eyes that underwent a reoperation achieved 20/40 or better, and 63 percent of them achieved 20/20 or better, and we show that compared to the pre-reoperation levels that was a significant improvement. We show that both in terms of the scatter and the mean the mean spheroequivalent improved to

very close to a zero target and so the accuracy of reoperation seems to be quite good, and they are effective at reducing refractive error and so in conclusion on reoperations we see that they are more common as the primary correction amount increases, that they have effective result in reducing refractive error and improving uncorrected visual acuity and that the risk of best corrected acuity loss is minimal for reoperations and that underscores the widespread clinical practice of having a certain rate of reoperations exist in a clinical practice of LASIK.

With this I will turn it over to Charles Casebeer.

DR. CASEBEER: This will just take 1 minute. I just wanted to review for all of you how this works out compared to the FDA guidelines, and I don't need to bore you with reading all of these things, but we were just extremely pleased to see that when we looked at the guidelines that we were able to put a check in every box, and that of course was the goal of the study and something that is pleasing, very pleasing to us.

So, in summary, we feel I think it is clear that the study exceeded the published FDA safety guidelines for safety and effectiveness and clearly nomogram adjustments with this particular laser are essential in LASIK and I feel and the other people at CRS feel that the approval of this

very popular, very exciting procedure is in the best interests of the public and of ophthalmology and again, thank you very much for allowing us to make this presentation before you.

DR. MC CULLEY: Does this conclude sponsor's presentation?

DR. CASEBEER: It does.

DR. MC CULLEY: I would like to thank you for a very clear presentation. I would like to poll the Panel now. Would you like to take a break now or would you like to wait and take a break, a break, one break this morning?

Break now, all those in favor?

(There was a show of hands.)

DR. MC CULLEY: It looks like the break wins. Prior to the break I would like to say something. We must be very cautious as we all know about conflicts of interest. That can go to the extent of a perceived conflict of interest. So, I would like to suggest or just remind the Panel that I am sure everyone knows that we are not to discuss PMAs under consideration in this or any others in this session with anyone including FDA staff or amongst ourselves, and certainly not with anyone who is not on the Panel would be included in that additionally.

There can be the perception of a conflict, and I

am not certain exactly how I personally feel about this, but with heightened concerns I would caution you against having extended conversations with individuals who are not on the Panel that might be perceived as a part of a conflict of interest or a conflict.

I am sorry, quite honestly to have to be making that comment but I think that given the environment as it is right now for individual protection that is probably something one needs to take to heart.

So, with that, my watch, and I may be wrong. Sally and I aren't the same, even. We are going with my watch. I have nine-forty-three. We will take a 15-minute break. We will reconvene at 3 minutes before the hour.

(Brief recess.)

DR. MC CULLEY: We are delaying just a bit while there is an AV hookup for overflow.

We will now begin deliberation once again on PMA P990010 with FDA presentation.

Dr. Waxler?

DR. WAXLER: Good morning. I am Morris Waxler, Chief, Diagnostic and Surgical Devices Branch, and I am limiting my comments to introducing Jan Callaway, the team leader, and she will have a few more comments.

MS. CALLAWAY: Good morning. I am Jan Callaway,

the team leader for the CRS PMA for the VISX STAR Excimer Laser System. CRS Clinical Research, Incorporated of Scottsdale, Arizona, submitted this application which was filed on February 23, 1999. The sponsor is requesting approval for LASIK for the correction of myopia between minus 1 and minus 14 diopters with or without astigmatism corrections ranging from .25 to 6 diopters. The primary panel reviewers for this application are Dr. Mark Mannis and Dr. Mark Bullimore. Panel input is required in this area because clinical judgment is required to evaluate the data. Your comments from the discussion today will help us in evaluating the safety and efficacy of the device for this indication for use.

The FDA team evaluating this PMA included the following reviewers: for engineering and Operator's Manual labeling Dr. Bruce Drum; for patient information labeling, Ms. Paula Silberberg; bioresearch monitoring was supervised by Dr. Jean Toth-allen; statistical reviews were done by Ms. Phyllis Silverman; and, clinical reviews were done by Dr. Bernard Lepri. I would like to thank those team members for the outstanding job they have done in review of this document.

At this time I would like to introduce Dr. Bernard Lepri, the clinical reviewer for this application.

DR. LEPRI: Good morning, Mr. Chairman, members of the Ophthalmic Advisory Panel, CRS members, FDA colleagues, industry representatives and public representatives. Today, I am going to present to you PMA 990010 LASIK for myopia and astigmatism applicant at CRS Clinical Research, Inc.

The information that I am going to present to you consists of specific concerns that FDA wishes to obtain the Panel's expert opinion in consideration of this PMA. Information specific to these concerns will be presented to assist the Panel in addressing FDA's questions. The device under question, under consideration was the VISX Excimer Laser Model C STAR.

A brief description of the investigation is up on the screen. It was a 6-month investigation of LASIK for myopic correction both with and without astigmatism.

Question No. 1, do the clinical data in this PMA provide sufficient patient follow-up of LASIK for the correction of myopia with and without astigmatism in the ranges indicated?

Next I will present a different picture of the stability data that provides you a little more information in making your consideration. The stability was calculated for both low and high myopic corrections for all eyes, spheres and spherocylinders. This table presents all eyes

attending all follow-up visits specified in the protocol. The change in MRSE of less than or equal to 1 diopter between the 1 and 3 month and the 3 and 6 month intervals was calculated along with the appropriate standard deviations and the 95th confidence intervals.

To support the calculation of the percent of eyes demonstrating less than or equal to 1 diopter change in MRSE the sponsor, also, provided the mean differences as you can see here. I will give you a moment to review that.

The next slide represents all visits for all eyes in the 3-to-6-month interval.

My question to you is what are the Panel's recommendations regarding the sponsor's presentation of stability data for LASIK in the refractive ranges indicated in this PMA?

The following information is presented in support of Question 3 which will follow the following review charts of data. The total number of eyes whose spherical error was greater than 11 diopters was 33 or 4.56 percent of the total number of eyes in the PMA cohort. The number of eyes less than or equal to 11 diopters was 690, and the total was 723.

The total number of eyes demonstrating a cylindrical component of their refractive error was 579. Of those 579, only 11 were over 3 diopters of cylinder. This

comprised 1.9 percent of all eyes exhibiting cylinder. A specific stratified analysis of the spherocylindrical corrections reveals the following: In the category of greater than 3 to less than or equal to 4 diopters of cylinder 1.6 percent, a total of 9 of 579 spherocylindrical corrections ranged anywhere in sphere from greater than 4 diopters to less than or equal to 13 diopters.

In the category of 4 to 5 diopters of cylinder 0.3 percent or 2 of 579 corrections were in the range of greater than 8, so less than 9 diopters of sphere.

A stratified summary of the MRSE of plus or minus 1 diopter at 3 months indicates that 70 percent are within 1 diopter for the greater than 7 diopter category of refractive errors and 95.8 percent for those less than 7 diopters. This graph portrays a comparison of the diopter stratifications for myopic corrections over 7 diopters and the proportion of eyes achieving an MRSE within 1 diopter, their intended outcome at 3 months. The Ns are noted on the bars for further information for you because the percentages don't tell the whole story, and the next slide portrays a similar analysis for the 6-month postop interval. Both graphs demonstrate the lower number of eyes in the higher refractive categories.

Question 3. Do the Clinical data in this PMA

provide reasonable assurance of the safety and efficacy of LASIK for the correction of myopia with or without astigmatism in the ranges indicated?

You have been told that there was the use of individualized adjusted nomograms and this was unique to this protocol. Specifically the individualized nomograms utilized CRS providing the original nomogram. After the first 20 cases the achieved correction at 3 months was compared to the programmed amount for each eye. The average difference between the investigator's outcomes and those predicted by the group nomogram over the entire range was called the personal calibration factor.

The surgeon then used an adjusted group nomogram called an individual nomogram which was adjusted by the PCF. Individual nomograms result from adjusting the group nomogram, not just the surgeon's outcomes directly. The group nomogram reflects the behavior of the laser over the full treatment range. The mean outcomes were adjusted to approximately one standard deviation below plano to avoid overcorrections. This resulted in an actual target of minus 0.3 diopters. The sponsors proposed the following labeling regarding the nomogram. The programmed amount indicates the average correction that can be anticipated but actual use may require individual adjustments of this amount. Tracking

of clinical outcomes is recommended.

Question 4. What are the Panel's recommendations regarding the data on the individualized nomogram used in this investigation of LASIK, and No. 5, does the Panel recommend including warnings in the labeling regarding post-LASIK corneal ectasia? And I would like to thank the sponsor for providing us with a very cooperative and detailed report of their data which facilitated our review in a timely manner.

Thank you.

DR. MC CULLEY: Does that conclude the FDA presentation?

DR. LEPRI: Yes, it does.

DR. MC CULLEY: Should we give the Panel the opportunity to ask questions of FDA at this point? We will bring sponsor back again after primary review. Does the Panel have any question for clarification of the FDA presentation?

DR. YAROSS: This is Marcia Yaross. I have a question for clarification as to precisely what is the product under review here? Is it labeling for this group of clinical investigators or is it labeling for the manufacturer of the laser? Could you clarify?

DR. MC CULLEY: In other words what is the device

under review?

DR. YAROSS: Precisely.

DR. LEPRI: The device under review is the VISX STAR Excimer Laser Model C for the correction of myopia via LASIK.

DR. YAROSS: Thank you.

DR. MC CULLEY: This is not site specific as one other IDE PMA had been?

DR. LEPRI: Could you repeat the question?

DR. MC CULLEY: This is not site specific laser model serial number specific?

DR. LEPRI: No.

DR. MC CULLEY: Dr. Bullimore?

DR. BULLIMORE: This is Dr. Bullimore. Is it, also, microkeratome specific?

DR. LEPRI: It is microkeratome specific. They only used one microkeratome.

DR. MC CULLEY: So, this is specific to the model of the microkeratome not as one other or as it might -- I have to be careful how I word this, as it might be worded that an approved microkeratome. It is specific microkeratome model specific.

DR. WAXLER: I think a little more clarification is I can try. It is true that the Chiron ACS microkeratome

was the only one used in this trial, but I do not believe that the approval will read specifically that the LASIK was approved with this specific device. There will be generic descriptions in the manual for a microkeratome. Otherwise we would be labeling somebody else's medical device for LASIK which I think would not be appropriate.

DR. MC CULLEY: Your opinion overrides.

DR. WAXLER: For the moment anyhow.

DR. MC CULLEY: Your clarification overrides.

Listen, life is tenuous even though you wear a flower in your lapel. It doesn't protect you always.

Does that answer your question, Dr. Bullimore?

DR. BULLIMORE: Yes, thank you.

DR. MC CULLEY: Dr. Pulido?

DR. PULIDO: I would like some clarification from Jan Callaway about the patient accountability concerns and how she feels about the fact that there was 43 percent exclusion of the data.

MS. CALLAWAY: I would like to bring up the statistician, Dr. Phyllis Silverman.

DR. SILVERMAN: I am Phyllis Silverman. I was the statistical reviewer for this. I labored long and hard over this exclusion, and I don't really consider it an exclusion as much as a stratification of the data. The results were

stratified by the group of investigators that had more than 80 percent follow-up and the group that had less, and all the data that was available for both of those strata were presented so that it is not that we ignored all of those other sites. There was a statistical comparison done of safety and efficacy for the PMA cohort versus the remainder cohort and there were no statistically significant difference, and if anything, as was mentioned this morning the remainder cohort did better. So, there certainly was no bias in favor of the device by doing this stratification.

So, I don't think you should really look at it as an exclusion as much as a stratification.

DR. MC CULLEY: Does that satisfactorily answer your question, Dr. Pulido?

DR. PULIDO: Yes.

DR. MC CULLEY: I am going to get it right. You have turned it so I cannot see it.

Oh, Rick Ferris.

DR. FERRIS: This is Rick Ferris. I have a question regarding this approach of dealing with clinics with inadequate follow-up, and it is a design issue and then maybe we can get to the problem I have with it. I have suggested even on this Panel before that it isn't necessarily a bad way of dealing with clinics that promise

to perform but then don't perform provided two things, I think provided two things.

One is that the randomization is done within clinic, and I assume that was probably correct, and the second is that the cut point of which clinics were going to be included and which were going to be excluded was decided prior to looking at the data, and if those things are true, then I think you still have a randomized comparison and as you say, you have a stratified, you can, also, do a stratified look both at those in that follow-up group and those with less good follow-up.

The problem I have with all of this is there is no statistical way of handling missing data that I know of. I think the quote is the only way to handle statistically to handle missing data is not to have any, and anything else makes presumptions, and the usual presumption is that the data missing is similar to the data that you have. You actually said something just a second ago that suggests that may not be true. What you said was, I believe, and I believe the data says the same, that the group that has less follow-up actually looks a little bit better than the group with more follow-up. Is that correct?

DR. SILVERMAN: No, the centers that had less than 80 percent accountability, those patients that did return to

those centers looked better than the other ones, and the underlying premise is that the reason those centers didn't have complete follow-up is that their patients that were doing well tended not to show up for their follow-up treatments.

DR. FERRIS: Maybe you have to say that again for me because I don't quite understand it. If they look better with less follow-up, it must mean that the missing information is worse because that would --

DR. SILVERMAN: No, it is not that they had less follow-up. It is just less patients came back for the 6 and the 12 month follow-up. It is not that they just came back for --

DR. FERRIS: The concern is that the patients who are having problems -- my concern here with all of this is not on the efficacy side. I don't think there is any doubt that this laser does something. It is just to me that cannot be the issue. It obviously does something. The question is, and it is pretty effective at doing it. The question is, and as we heard earlier if we have a small amount of harm and we are trying to balance the benefits with the risks or give some assessment of the risks, the most conservative assessment of risk is that all of the people who didn't come back had a problem. Well, if you

took that point of view then you could have a fairly large problem. I think that is a ridiculous assumption. I don't think all of the people that didn't come back had a problem, but what you look for is is there some suggestion that those who aren't coming back aren't coming back because they are having a problem or is it just that the people who are really doing the best are so happy and why bother coming back, and then you worry less about it, but we don't have any way of handling that, and I think that is the concern that the bigger that portion is that we are missing if we are looking for balancing a small negative effect or at least trying to allow the patients to know what the degree of negative effect is, when there is a lot of missing data it is very difficult to assess that.

DR. MC CULLEY: Let me interrupt here? We are getting our agendas mixed. I think what we want to do right now is, I mean you bring up a very valid point that we need to have as part of the Panel discussion. What we want to do right now is if you want to challenge or have a question or any of us for FDA to respond to, this is the time for that.

DR. FERRIS: I have three questions. Question 1, and I saw some nodding. So, I think I know what the answers are.

DR. MC CULLEY: Let us get FDA response. State

your question briefly.

DR. FERRIS: Question 1 was did they pre-specify that 80 percent was the cut-off and clinics that had less good follow-up than that would not be included, and the reason that that is a problem, it ought to be obvious --

DR. MC CULLEY: You could move the cut-off. So, answer that. That is a simple question, yes or no?

DR. LEPRI: Bernie Lepri. To the best of my knowledge they did not pre-specify, and they can correct me on that. This was established when they observed the compliance rate of the investigators.

DR. MC CULLEY: Okay, we will discuss that when sponsor comes back then.

Second question?

DR. FERRIS: Second question, did they randomize by clinic? I assume they did, but I don't know. Within clinic they have a randomization schedule, and you can randomize --

DR. MC CULLEY: There was no randomization.

DR. FERRIS: Oh, I am sorry. So, everybody got treated. Boy, I did clinical trials too long. So, I mean that would be the other issue, and the third question, well, we will get to it later. That is part of the discussion.

DR. MC CULLEY: Right. The issue I would have with

this would be what did the data look on the missing patients that weren't there at 6 and 12 months.

DR. LEPRI: That I can address. I mean they did provide a last visit carry forward analysis and there were no glaring differences in outcomes between those presented in PMA cohort and remainder cohort. They provided a complete detailed information on those patients.

DR. MC CULLEY: Questions for the FDA to answer?
Dr. Wang?

DR. WANG: Ming Wang. I have a question for the statistician of FDA. I am struck by the lower numbers above minus 11, minus 12 and if you have only a couple of patients the very little statistics that can be talked about. Does FDA feel that there is need to be someone look at that particular group separate because results also, fall off sharply at minus 11, minus 12 or higher? Does percentage eigne anything in that specific group with such a small number in terms of quality of statistics?

DR. MC CULLEY: I am not a statistician, but I can answer that. Does the statistician want to answer that?

DR. SILVERMAN: I didn't see any glaring differences, but I felt that was really more of a clinical issue than a statistical issue.

DR. MC CULLEY: Dr. Rosenthal?

DR. ROSENTHAL: This was one of the questions asked about the range. So, you are asking the Panel's recommendations concerning this?

DR. MC CULLEY: I think when you have such small numbers we are not going to be able to answer it statistically. It is going to be clinical judgment. That is why we are here with our minds.

Any other questions for the FDA to answer?

Dr. Macsai?

DR. MACSAI: Was the 80 percent cut-off set by you or the sponsor, going back to the accountability question?

DR. LEPRI: It was set by the sponsor.

DR. MACSAI: Was it, also, looked at at a 90 percent accountability cut-off?

DR. LEPRI: We will have to ask sponsor. Sponsor said it will have to ask sponsor when sponsor comes back to the table.

DR. MACSAI: I was wondering if the statistician had looked at it like that? No? Thank you.

DR. MC CULLEY: Dr. Higginbotham?

DR. HIGGINBOTHAM: This is a question for Ms. Silverman. In your report, you noted that there was a poor success rate for the 7 high myops in the smaller centers and that was 15 out of 36 or 41.36 percent. Was there

additional data provided that would suggest that over time those patients improved or was this the ultimate that you actually noted, this 41.36 percent?

DR. SILVERMAN: Was that with the centers that had the combined centers that were --

DR. HIGGINBOTHAM: Yes, there were seven myops treated at center 22099.

DR. SILVERMAN: Right and they had a --

DR. HIGGINBOTHAM: It was the high myops at the combined centers.

DR. SILVERMAN: At the combined centers?

DR. HIGGINBOTHAM: Exactly, and you noted --

DR. SILVERMAN: I felt that that probably was due to a learning curve effect, that that was a combination of about four or five centers that had very few patients treated and I felt that was probably a learning curve phenomenon, and I didn't see any additional follow-up on them. It might have -- the sponsor may have it, but I didn't. I am not aware of that.

DR. HIGGINBOTHAM: So, there was no additional follow-up. That was my question. Thank you.

DR. FERRIS: One last question for FDA. Is there any differentiation in the data between the patients that were treated, the first 20 patients treated by a given

investigator and those done after the nomogram was individualized or are they all pooled together?

DR. LEPRI: Bernie Lepri. They were all pooled together.

DR. MC CULLEY: We will have opportunity for further questions subsequently. We are going to pause in place for 3 to 5 minutes for an audio hook-up to be accomplished. We are not going to break because breaks tend to expand.

Are the folks who want to do the audio hook-up ready to do it? Okay, so there is going to be minor distraction. So, official business will be paused for the moment.

If you will tell me please when you won't be a potential distraction we will proceed, audio folks, please?

Let me know when you are not going to be going back and forth in front of us, please let me know so we can go ahead?

(Brief recess.)

DR. MC CULLEY: We have given them quite a few minutes. They are still in the process of hooking up. We are going to proceed with our deliberations. We have a new procedure in that one of the primary reviewers will be asked to keep track of recommendations, concerns that the Panel will specifically be making. So, we will have a designated

scribe for PMA, and Dr. Bullimore, I saw you raise your hand.

(Laughter.)

DR. MC CULLEY: I saw something waving down there. So, I assume that you were asking to be designated. Would you please do that for us?

DR. BULLIMORE: My mother is in the audience.

DR. MC CULLEY: She will be proud, I hope. That means you have got to do a good job. We will now begin with the committee deliberations, and we have two primary reviewers, Dr. Mannis and Dr. Bullimore, and we are going to ask Dr. Mannis to go first.

DR. MANNIS: Thank you, Dr. McCulley. You chose the right Mark. First, I would like to thank the FDA for the usual businesslike manner in which these matters are handled, and this represents information for the sponsors and for the American public.

I would, also, like to extend my thanks. As you all know this process is a series of distillations. The FDA is presented with a mass of data from the sponsor. The FDA's staff then goes through this data and does a clinical and statistical review for the primary analysts, and it is our job then to reassess that distillation and try to put it in a meaningful form for the Panel.

Sally has asked us to be brief, and you all have my own distillation in comments in writing in front of you, but I would like to make a few points and prior to that I would, also, like to thank Dr. Lepri for a really masterful compilation of this data. It made it very, very understandable, and I would, also, like specifically to thank Phyllis Silverman whose analysis I thought showed a great deal of insight and clarity. In terms of the primary issues at hand we are dealing with issues of efficacy and safety. The data based on FDA guidelines certainly suggests that the procedure is efficacious in terms of the goal sought in terms of predictability, in terms of stability over the 6 month observation period and in terms of effectiveness in the modulation of corneal astigmatism.

Five parameters as pointed out by Dr. Kezirian were used to assess safety in terms of less than 5 percent loss of greater than 2 lines of best spectacle-corrected visual acuity. Essentially all groups met the target. In terms of the goal of less than 1 percent of best corrected spectacle visual acuity of less than 20/40 there was a division and unless I misread the statistics 7.1 percent of patients in the greater than minus 7 diopter group had a best spectacle-corrected visual acuity of less than 20/40 at 6 months. So, in this case the safety parameter was not met.

Haze and induced astigmatism as pointed out were not an issue and in terms of adverse events the only adverse event that significantly was outside of the FDA parameters was a 1.6 percent incidence of interface epithelial inclusions which were felt to be non-significant clinically.

If you look at this data overall, I think there are two issues which bear significantly on the way the Panel should label this application. First is that the groups need to be divided and looked at carefully into between that group of patients equal to or less than minus 7 diopters of myopia versus those greater than 7 diopters. Not only was at least one safety parameter exceeded in the greater than 7 diopter group but in addition, if you look at the rates of uncorrected visual acuity in the below minus 7 diopter group, 54 percent had 20/20 at 3 months, whereas in the above 7-diopter group 35 percent had 20/20 vision.

If you look at 20/40 vision as a parameter, 94 percent of those under 7 diopters had 20/40 and 79 percent in the group above minus 7 diopters. So, clearly there is a dividing line in both efficacy and safety at the 7-diopter level. I think that this should probably be reflected in the labeling recommended by the Panel.

In addition, the sponsors indicated to us that symptomatically based on questionnaires the two groups were

equal. However, doing some quick math this morning during Dr. Kezirian's presentation 20 percent of the patients were subjectively worse in terms of glare. Now, we weren't told at what level, whether that was dysfunctional glare or noticeable glare but there was clearly a 20 percent incidence of some visual dysfunction and although not mandated one does give pause to concerns that perhaps non-acuity parameters should be evaluated over the entire range of refractive errors in this procedure.

Overall, my impression of the study design was that it was both well designed and executed, that the cohort was of a suitable size and that unless the Panel determines that the deletion of the 43 percent in the non-PMA group based on compliance at the 3 months becomes an issue of pre-selection, I feel that the data in the PMA cohort justifies the overall safety and effectiveness of the procedure.

I think that in deliberating the label I would say that the degree of myopia should be an important consideration and the issue of a nomogram should be important. The nomogram in this study was based, the group nomogram was based on a non-IDE database which was then modified by this personal calibration factor after 3 months when each investigator had done 20 cases, and I think that the data suggest that this is useful way in which to

construct a nomogram, but that nomogram construction has to be reflected in the labeling.

In summary then I would recommend approval of the device as safe and effective for the treatment of myopia with or without astigmatism in the indicated range. Because of the small numbers in the study, I feel that patients with spheres or spherocylindrical corrections of greater than 10 diopters may experience complications that were not elucidated, and this needs to be clear in the labeling. I feel that iatrogenic corneal ectasia which is obviously one of the most serious complications needs to be specifically cited particularly in the higher myopic group.

Because of the nomogram issue which is as pointed out necessary in the clinical performance of all refractive surgery, LASIK included, the labeling should include that the programmed amount of treatment indicate an average anticipated correction but that actual use will require adjustments based on tracking of clinical outcomes by the using surgeon, and finally, that in patients over 7 diopters of myopia the accuracy cannot be as clearly guaranteed as in lower myopic patients.

Thank you.

DR. MC CULLEY: Thank you, Dr. Bullimore?

DR. BULLIMORE: Thank you, Mr. Chairman. This is

Mark Bullimore. I don't want to go into the data too much since both the sponsor and the medical officer have already given an excellent overview of that.

Like Dr. Mannis I believe the PMA is approvable with some conditions that relate to product labeling and the range of approval, but there are a number of things that I would like to bring to the Panel's attention for discussion.

The biggest is this issue of accountability, and Dr. Ferris has already raised this, and it already has had some discussion among the Panel. One characteristic of the PMA is the very variable accountability of these clinics. Overall the accountability is less than 75 percent at 3 months and less than 63 percent at 6 months, and if you look at the data, one surgeon actually enrolled 179 patients which actually represents 10 percent or more of the entire cohort but did not report any 3-month examination. So, at least in that particular surgeon's case there is no bias, but the sponsor addresses the issue by dividing the whole cohort into this PMA cohort and this remainder cohort.

I was, also, intrigued to note that of the three people who made presentations to the Panel, the three physicians, one of them wasn't included in the PMA cohort and a second actually just made the cut.

So, this is a constant source of concern for me

because as indicated by Dr. Ferris, we know something about the people who do return for the visits, the follow-up visits, but we never know anything about the people who don't return. We can say that the PMA cohort that return are reasonably equivalent to the people in the remainder cohort, but the individuals that are included ultimately in both cohorts and taking the cohort as a whole we don't know anything about the 30-something percent who are not seen at 6 months.

So, the potential for patient bias or surgeon bias or investigator bias is considerable because of this at best mediocre accountability.

I was interested to hear the comment made that when you do compare the PMA cohort, that is the good clinics with the remainder cohort henceforth referred to as the great unwashed, that does suggest that there is some bias there on the part of the physicians, and I don't want to sort of target them or be accused of slander, but the fact of the data they are reporting, given their lower accountability is slightly better than the group, the PMA cohort, suggests that the bias actually runs in that direction. So, that is all I have to say about that, and we have an industry representative on the Panel, and I wouldn't expect that many of the investigators would get a call from

Dr. Yaross for her own company's investigations given some of these rates of follow-up.

In terms of efficacy, I think that is the strongest part of the proposal, both in terms of sphere and SIL(?) the laser clearly does what it is intended to do. The question remains whether it should be approved for the higher ranges of myopia.

Although the sponsors request an approval for up to minus 14 diopters, I believe that is spherical equivalent but I would like some clarification, but by their own admission the distribution of refractive errors tapers off beyond minus 11. We only have 29 patients reported at 3 months in the minus 11 or greater range and only 17 with more than minus 12 diopters of myopia.

The problem is just as acute and maybe more acute for astigmatism. Approval is being requested for up to 6 diopters, but only 11 cases are reported over 3 diopters and only 2 patients had greater than 4 diopters of astigmatism.

So, in summary I would ask my colleagues on the Panel to consider what the entire range for approval should be.

The range of approval, also, has relevance to the question of corneal ectasia, and there are a number of reports and comments in the literature by very distinguished

people in the field about the risk of corneal ectasia above minus 10, and minus 10 seems to be a line drawn in the sand, and I would have difficulty based on the data here going beyond minus 11, certainly not minus 12.

Stability refraction seems to be okay. There seems to be little average change although the patients with higher degrees of myopia seem to take a little more time to reach stability.

I would point out the potential for long-term changes in refractive error does still exist. Only going to 6 months would not, for example, demonstrate the long-term hyperopic shifts that we saw in the Perk(?) study. So that possibility remains given the limited amount of follow-up.

Frequency of loss of visual acuity is low, and that is within guidelines. As Dr. Mannis pointed out, there are a number of people who in the higher myop group end up worse than 20/40 and I will accept the sponsor's observation that many of these started with visual acuities, best corrected vision acuities of close to 20/40, but they, also, of course, do have the benefit of the magnification induced by moving the refractive correction from the spectacle plane to the corneal plane.

Sixty-four of the PMA cohort were excluded due to, from the 6-month visit, due to retreatment. Since

retreatment does occur in a significant proportion of the cohort some analysis of the safety in this group which I think has already been presented is appropriate, and should be included in the labeling.

It is, also, unclear to me from the original proposal how stable pre-operative refractive error was defined. So, some clarification would be useful there, and as I have said at a previous meeting there is still need for a standardized questionnaire or instrument to be used for the assessment of patient satisfaction following these procedures.

Interpretation of data from different sponsors would then become a little more meaningful.

Thank you.

DR. MC CULLEY: Thank you.

Just an editorial comment. It seems like the accountability here is an issue as it has been in other situations and we have a standard that is set. This isn't a brand new device in one sense, and it is not our first experience with it, and I think that to me a real question is the patients that weren't present at 6 and 12 months with us seeing stabilization in general toward 3 months, what is the accountability at 3 months, and if we have good accountability at 3 months given the appearance of stability

at 3 months, given the overall experience that I think we bring to the table, then I would be less concerned about the accountability from a practical standpoint but from an idealistic standpoint I certainly would not want to send a message that long-term, when there are issues, this kind of accountability is acceptable.

Is that fair?

DR. MACSAI: Dr. McCulley?

DR. MC CULLEY: Dr. Macsai?

DR. MACSAI: This is Dr. Macsai. In your statement you just that as long as stability is established at 3 months. I am not sure --

DR. MC CULLEY: I said, "Stability appears to be established at 3 months in this" --

DR. MACSAI: If accountability is inadequate and stability is established by measuring two different points at a set time period and comparing those two how does one establish stability?

DR. MC CULLEY: I don't want to argue the point, Marian, but what I am saying is that if we have stability established at 3 months, if that appears to be the case, part of my statement was a question. If indeed stability appears to be established by 3 months and we have good accountability at 3 months, I am less concerned about the

drop-off in accountability at 6 and 12 months with this particular device or with Excimer lasers that we now have a good deal of experience with. It is not a device coming in that is not in the market that we don't have experience with and that many of us have experience with. That was my comment because I think we can slam dunk this PMA based on accountability.

So, what I am trying to do is let us get to a meaningful discussion about accountability or else we can go on forever about it because it is not good as we get into the later time points, and we need to use our time effectively and decide how we are going to deal with that issue.

I said one way that to me I thought was a reasonable way to deal with it, with this particular device. The biggest risk I see in that is that being interpreted as setting some kind of precedent where we don't have any degree of comfort level or knowledge that we do have here, and I just want to be absolutely clear that we don't do that and quite honestly that would affect how I would feel if I thought that would establish something that would come back to haunt us in carrying out effective deliberations in the future.

Dr. Pulido?

DR. PULIDO: Jose Pulido. First, Jim, for the remainder cohort the accountability was 57.5 percent at 3 months. So, even there the remainder cohort had --

DR. MC CULLEY: What about the other cohort?

DR. PULIDO: The other cohort was 90 percent. For the record I just would like to state the following. I agree that the data from the PMA cohort shows very good safety and efficacy in patients with astigmatism up to 3 diopters in myopia up to 10 diopters but I have strong concerns regarding accepting the study as a whole because of the data set and if the FDA accepts this kind of study where accountability is only 57 percent, only because there was a large number of patients where will we stop? If there is a subsequent study where enrollment was 10,000 and there was good follow-up on 1000, will this be accepted? The doctors should be chided for bad science, and if they enroll patients into a study, they should be ethically bound to follow up on these patients.

DR. MC CULLEY: I think we need to continue to discuss this issue a bit now because I think this is the most critical issue.

Dr. Wang?

DR. WANG: Ming Wang. Along the argument of this issue, since I first raised the issue about whether this was

preset or not obviously there is the question of bias on whether the 80 percent was set depending on where the lever was set, and since the primary data is all there, the elements are all there, could we ask the sponsor to look at whether say, set at 70 percent or 65 percent will a totally different type of conclusion be drawn, and we can determine whether this setting is somewhat a sensitive issue?

DR. MC CULLEY: Dr. Bullimore?

DR. BULLIMORE: Yes, this is Dr. Bullimore speaking as a primary reviewer. I think that is an intriguing idea from a scientific point of view, but the fact that there is no difference in the safety and efficacy outcomes between the two cohorts when the criterion is set at 80, I don't expect the change in the cut point is going to provide us with illuminating information. It might be useful, but I think it would appear as sort of busy work or punishment for the sponsor rather than being illuminating for the Panel or the FDA. So, I would discourage that particular line of pursuit..

DR. MC CULLEY: Dr. Ferris?

DR. FERRIS: I think going in that direction you already have a pretty good estimate of what is going to happen because you looked at the two cohorts. So, as you lower the bar further it doesn't hurt the assessment. In

fact, it is in favor of saying that it is safe and effective. The concern is what happens if you raise the bar and look at only those clinics with 90 percent or 95 percent. I assume if it wasn't predetermined, the 80 percent that they way they determined 80 percent was the balance between the N and as you take that bar higher, now the standard errors around all these estimates are going to become more of a problem, and I presume that that is why they did this.

This application to me is interesting in that I think the surgeons have done a marvelous job in one sense. I mean on their own they have gone ahead and done this at their own expense.

The unfortunate part was that at least some of them and maybe most of them didn't really understand how important it was at the beginning to make sure that those patients they entered in the trial understood that they needed to come back, that if they didn't come back it was going to really jeopardize the whole program, and that is my view, that it jeopardizes the whole program.

I sort of agree with what you said, Jim that in this case it is a little bit different than the usual kind of situation we have. I would find it very disturbing if people went away from here if this was approved and they

thought that we only need 80 percent follow-up because I don't want to be part of lowering that bar. I think the bar ought to be raised, if anything.

On the other hand, the last time I -- actually driving in here I heard a number of advertisements for this procedure. So, I am not sure. I thought to myself well, people little note nor long remember what we do here because as near as I know this train is moving.

DR. MC CULLEY: I think that the risk to us is exactly what you and Dr. Pulido said. If we can rationalize this that the core had 90 percent at 3 months and at 3 months we had stability we bring our reason to the table rather than our ruler to measure risk with; then we can rationalize it if we are comfortable with everything else, and I think we have to decide whether that is what we want to do now or not because that is what everything else hinges on.

DR. YAROSS: This is Marcia Yaross. I think you spoke a moment ago, Dr. McCulley about the message that goes forth from this Panel. I think one of the messages that intended or not is sometimes perceived is that there are different standards for investigator-sponsored PMAs brought to this Panel than for industry-sponsored PMAs, and I think that is something the Panel should be aware of.

DR. MC CULLEY: I think that is very good that you stated that. I can tell you from my perspective I try to be as consistent as I possibly can be, but we wouldn't need to be here, and we could have computers in our place if we weren't meant to bring our reason with us and our experience. So, that may be the perception, but I guarantee that sure is not the intent, and people aren't paying attention, to me, if they think that.

Dr. Van Meter?

DR. VAN METER: There is another data issue that clouds the results for me, and since you mentioned experience, I take this time to bring it up. We have spoken for years about the importance of learning curves and the idea that some experience is helpful in doing this procedure. We, also, have an admission, by the way, that sponsors have gathered data that after 20 cases an individual fudge factor is necessary to alter some of the treatment parameters and yet all of this is pooled, all the patients before and after the, you know, first cases and last cases are all pooled together, and I think it is fairly important to look and see if a learning curve is important because I think this is critically important in determining how you are going to train surgeons to do this procedure because everybody is going to have a learning curve.

DR. MC CULLEY: The reality is that there are LASIK training courses going on now, and my impression is how those are dealt with is that surgeons until they get their own information, I mean the nomogram in effect is somewhat surgeon surgical technique dependent. It is environment where the laser is housed dependent. It is laser dependent and then those we can kind of deal with with our experience, but it is somewhat patient and eye dependent and the approach, taking everything possible into consideration is to aim to under correct and then as one gets personal experience with that laser in that environment with that surgical technique to start to move upward and the incidence of retreatments decreases. If we remember previous data we have had retreatment rates in the 40 percent range.

We now have a retreatment rate, I don't remember the number, but it is somewhere in the 10 percent or less range. So, I think that that is where we come back to, if we get over the accountability issue, we have to address the labeling on the nomogram.

DR. MANNIS: Jim, just a point of clarification. I am sure we all understand this.

DR. MC CULLEY: Dr. Mannis, please, always identify yourself?

DR. MANNIS: Mark Mannis. These were not their

first 20 LASIK cases. They were the first of the 20 cases they did in the study. I think that is important for the record, that the surgeons who participated were all experienced LASIK surgeons.

DR. MC CULLEY: Okay, I think we need to -- yes, Dr. Pulido?

DR. PULIDO: I understand that as anterior segment surgeons you have all had the experience that this is a good technique, that it needs to be accepted. On the other hand, and Rick Ferris can correct me, and you are going back to the experiences saying, "Well, we can accept this data because our experience says that it is so," but Rick Ferris may correct me if I am wrong, when the original DRS was going to come out, they polled the doctors as to what the results were going to be about laser photocoagulation which we know is efficacious now for diabetic retinopathy and the experience of each doctor was the majority thought that the study was going to show that laser photocoagulation was of no help in these patients. So sometimes experience may not be the right role in large studies like this.

DR. MC CULLEY: Dr. Ferris?

DR. FERRIS: Rick Ferris. It was actually in a macular photocoagulation study, and I think the difference there was that the treatment effect is relatively small, and

so, it is easy to make a mistake.

In terms of the treatment effect here, I assume that that mistake isn't being made, that if you ask these surgeons and the DRS, by the way, I think one of the clinics thought the treatment wasn't helpful, and the others thought it was, but there it was a 50 percent treatment effect compared to a smaller effect although the short-term effect with macular photocoagulation is about 50 percent.

The issue remains though as to whether we are sending any message, and maybe at the very least we have to make it clear that this decision is based not just on this data, that it is a serious fault, that there is this much missing data. In fact, I got very frustrated reading this and thought to myself, why don't they just bring up patients and have little anecdotal reports because this data in my view as a scientific study is something in between anecdotal reports and what you would call an adequate scientific study, and the fact that there is even the 15 or 20 percent missing information when we have bars that say you cannot have more than 5 percent of this or 1 percent of that, that missing information makes it very difficult to interpret whether you have really made that or whether you have somehow with regard to bias excluded the worst cases and if anything I still believe the data tend to suggest that the

worse the follow-up is the more likely that sort of the better the group is and you know, when you look at that remainder cohort versus the, unless I have it wrong, versus the main cohort the remainder cohort does better and what that tells me is that as you added more patients you are reducing the mean and suggesting that the missing information might be in the direction of harm or at least less efficacy and that is the concern, and there is no way of dealing with that missing information that I know of.

DR. MC CULLEY: Dr. Matoba?

DR. MATOBA: Alice Matoba. I am relatively new to the attendance at these meetings. So, excuse me if this is already known, but does the FDA set these criteria for accountability up front?

DR. MC CULLEY: In the guidance document there is a target, yes.

DR. MATOBA: Ninety percent. So, okay.

DR. MC CULLEY: But it is not an absolute. I mean it is a guidance.

DR. MATOBA: Shouldn't there be some absolute number that should, also, be set?

DR. MC CULLEY: In a perfect world, yes, but it doesn't seem to work. I don't know that I can rationalize that or make good sense for you, but just to tell you it

doesn't seem to work. It would be nice to have an absolute, that if it doesn't reach that we are not asked to add our knowledge and wisdom to it.

Dr. Bullimore?

DR. BULLIMORE: In the interests of moving the discussion along, I am happy to accept the data as they are presented and move on from this accountability issue. I know I made some fairly strong statements about it, but I think they have been made, and we can move forward to address the question raised by the agency.

DR. MC CULLEY: Is there disagreement with that position and if so I would like for you please to state it now?

Dr. Macsai?

DR. MACSAI: In response to Dr. Matoba's inquiry in the checklist for information usually submitted in an investigational device exemptions application for refractive surgery lasers dated October 10, 1996, accountability is as follows: The loss to follow-up typically should not exceed 10 percent at 1 year, and I have a great deal of difficulty with an accountability of 50 to 76 percent at 6 months.

DR. MC CULLEY: Okay, Dr. Macsai has basically as I understand your statement stated disagreement with Dr. Bullimore's assessment.

Does anyone else have a disagreement with that?

MS. MORRIS: Lynn Morris. I guess I just have a question. How if you accept this level of accountability is it not setting a precedent?

DR. MC CULLEY: Again, I said that before. I can restate it. Basically we are asked to bring our experience, knowledge to the table. I am not trying to argue one side or the other here, but if we have 90 percent accountability at 3 months, stability established at 3 months given all of the information available to us that that is it is possible for us to consider that as a reason to consider the data as presented otherwise. We have to decide whether that is reasonable or not, and everything else hinges on that, and we need to decide that. Otherwise, well, we need to decide that.

MS. MORRIS: So, I guess my question to take it to the next level is if you determine that now when we come back to make a determination on another PMA in the future, isn't there, I mean couldn't the sponsor argue that we accepted this level of accountability?

DR. MC CULLEY: Not really. I think we have to -- PMAs are not done one in comparison to the other. It is a sticky point, and yes, I mean it is risky, and I see that as the biggest risk in accepting the data. I agree with that

concern, and it is just a matter in the minds of the members of this Panel as to how they weigh that, but each PMA stands on its own bottom as I understand it, and we do not compare in making decisions about a PMA we are not making comparisons to others. We are bringing a set of knowledge to a set of data and the experience of a group of people to the table. All of those change from one PMA to another. We change. Dr. Bullimore pointed that out once, that when something was being said to us, that he wasn't at that particular meeting or something of the sort, but the people change. We are not on this until the day we die and even if we were, we would still die and have to be replaced.

Dr. Van Meter?

DR. VAN METER: Woody Van Meter. Because the sponsors have adequate data for the main cohort is because they have carved out the additional cohort. Even though it looks like the patients in the additional cohort did well, I think that that is not science to carve out data that is not compliant. I don't think, it is not, I mean I think in the past we have asked the sponsors to come up with data to meet that criteria and I believe that since there is such an effect here that whether it is by telephone or letter or what not, that data is out there.

DR. MC CULLEY: And we have done that, and we have

accepted funny statistical machinations that are beyond my ability to understand in the past as well. What we need to get is a sense of where we are going.

Dr. Rosenthal?

DR. ROSENTHAL: I would just like to make two comments. The first is that the guidance is guidance, and as you know the office has I think quite publicly stated that in general for the Office of Device Evaluation an 80 percent level is generally acceptable of accountability.

The second is an issue that when you consider your deliberations in the PMA you do it based upon all the information, not only that is presented to you but that is going on in the outside world.

Now, this is a procedure that is being, and I am not arguing one way or the other. I am just presenting something to you. This is a procedure that is being done quite extensively throughout this country in which there is no information publicly available except what doctors want to give to patients based upon off-label use. It is the practice of medicine. It is not being done one or two times. It is being done thousands of times, and I think part of your deliberation has to be you have to weigh the issue, that is it important to have some information even though it is not perfect science, and that is your decision that one

has to make.

DR. MC CULLEY: Dr. Sugar?

DR. SUGAR: Joel Sugar. While I abhor the exclusion of a substantial number of patients and think it is inappropriate, the accountability, also has to be seen in light of the safety and efficacy, and if there were serious questions about safety and efficacy, the level of accountability that we would demand I think would be higher.

I think that the data presented plus as Ralph mentioned the experiential data that is available outside of this application suggest that it would be wrong I think to disallow this PMA based on the accountability as it is presented and that we should proceed to move forward and have some impact on this procedure by approving this with modifications and move beyond this issue.

DR. MC CULLEY: Dr. Wang?

DR. WANG: Ming Wang. I would like to echo some of those things already expressed. I agree that we should be very careful not to set a precedent but overall as an anterior segment surgeon who has done 2000 LASIK cases myself I have a basic hunch this is a good procedure with adequate efficacy and safety. I would recommend to go beyond this issue but do make some kind of language so that to specify the FDA is not totally happy with the

accountability in this particular study and restate our need for a good scientific study that higher accountability is required.

DR. MC CULLEY: Dr. Mannis?

DR. MANNIS: Mark Mannis. I have a question that may be naive, but is it possible for the FDA to request the sponsors to provide us with follow-up information on the 43 percent non-PMA cohort even though it is not at 6 months? Could they resurrect those patients and so to speak and could we get that information? Could it be conditional upon that?

DR. MC CULLEY: Dr. Rosenthal, would you like to answer that?

DR. ROSENTHAL: Certainly if the Panel deemed it so it could be a condition of approval.

DR. FERRIS: This is Rick Ferris. I was happy to hear what Dr. Rosenthal said because it seems to me that the public health issue here is as great as the issue as to whether this laser works or not. I have heard advertisements suggesting that there are no side effects to laser and I take it that if this was approved and there are documented levels of side effects that those advertisements would no longer be appropriate. So, I think we have to be careful about going too far in the other direction and

trashing this because there is a public health implication of saying nothing, and if we defer saying something the only comment I would have is that my concern is that I don't know what the complication rate truly is lurking out there. You know, we had suggestions this morning that it may be higher than we think. As a retina person I have to see the data, and the problem is that this data cannot tell me what that rate is. It can tell me what I think the lower limit of that rate is but not what the higher limit is and whatever we say I think might be that to me the complications that we see here may well be the lower limit of the complications. They may be somewhat higher.

DR. MC CULLEY: In my experience the complication rate that they reported is what others are reporting in other venues.

DR. FERRIS: But even there the problem, I don't know whether, I assume that the rate of people coming back for them is similar to the rate of people coming back for new and so nobody may know what the lurking complication rate is, if the disgruntled don't come back, and that is the issue.

DR. MC CULLEY: Okay, we need to stay on this, and there may or may not be those issues with the other reportings. I don't want to get off on that. They are not

necessarily there.

Dr. Van Meter?

DR. VAN METER: What we could do is fine with me. I mean the issue is whether or not we want to get more data, and we can discuss that at the tail end, but there are lots of other issues about safety and efficacy especially in the higher groups, and if you want to summarize what the Panel thinks about this issue, would you want to --

DR. MC CULLEY: We will do that when we come back to the specific recommendation. At least my sense of this which I guess unfortunately we have to rely on to a degree is that we more or less have the issue fairly well dealt with and we will formally deal with it when we come to answering the question for the FDA, and I think now we need to move on to other issues, but I think that what I would like to do now is invite sponsor back to the table for Panel to ask the sponsor questions about data that they have presented.

Would sponsor like to return? This is a time for clarification. Sponsor is not to take this as an opportunity to present other data. It is a time for Panel to ask the sponsor for clarification on issues that have been presented.

So, Dr. Sugar?

DR. SUGAR: Joel Sugar. Dr. Kezirian, you stated that 7 to 8 percent, 7 percent in the lower and 8 percent in the higher myo group had reoperations. How many of those were for refractive purposes only and how many were for wrinkles, epithelial ingrowth or whatever?

DR. KEZIRIAN: It was approximately two to one were for refractive errors and the rest were for epithelium or wrinkles, caps and that sort of thing, two to one for refractive.

DR. MC CULLEY: I thought that, Mark in your review you said that the epithelium was minor and that they weren't reops for epithelial ingrowth. So, I am confused.

DR. MANNIS: That is what I understood. I must have misunderstood.

DR. KEZIRIAN: No, there were some that were lifted for epithelium.

DR. MC CULLEY: What percentage?

DR. KEZIRIAN: I would have to get back to you in the next section on that to give you the absolute number.

DR. MC CULLEY: Does the FDA have that data at hand from your analysis, that piece of information, percentage of flaps lifted for treatment of epithelial ingrowth?

DR. LEPRI: Mr. Chairman, Bernie Lepri. I do not

have that data available. We would have to look it up.

DR. MC CULLEY: That was not in our package, the best that I could tell. One other question. Was pupil size looked at apropos of the public comments?

DR. KEZIRIAN: Pupil size was not one of the considerations in this protocol.

DR. MC CULLEY: Dr. Wang?

DR. WANG: Ming Wang. A question for sponsor. The pockets in the results in the above minus 7 correction range that fall out of FDA guidelines even though most of the data fit the guideline and there is obviously good statistics at minus 7, poor statistics at minus 15 or 13, let us say. I guess it was upper limits of 14. Do you have a feeling what is the threshold in which the statistics become not good, somewhere around 10 or 11 because that will give a basic measure of confidence in the data.

DR. KEZIRIAN: I appreciate the opportunity to address this issue because I think that there are a few considerations that have not been brought to light that should be in order to consider this well. First of all the one target that wasn't met which was the best corrected acuity exceeding 20/40 in the greater than 7 diopter group did not occur in many eyes. We had four eyes we were looking at it, but the N tapers off toward higher

corrections as you noted. So, that becomes proportionally heavier weighted. So, it wasn't something that occurred in a large number of eyes, and it wasn't something that occurred in a trend. If I saw it occur in a trend that you know you had one in the 7 diopter bin and two in the 8 diopter bin and three in the 9 diopter bin even percentage-wise was increasing as you went higher I would have much more concern than I do when I see it occur in four eyes that were clustered between 9 and 11 diopters and did not occur in the eyes that were higher than that. So, I don't know that I accept de facto that a safety risk for best corrected acuity loss as we measure it occurs in a trend with higher corrections.

Now, why? Perhaps because it was protected against with some of the things that were done in the exclusion and inclusion criteria. It may be that we are guarding against them, and we are protecting as we should be against those things. So, regarding safety I don't have a clear answer for you. My feeling is that through the range of the study we were safe. Effective, I think efficacy again has to be considered in the issue of this nomogram that Dr. McCulley talked about a moment ago.

We intentionally as you saw in the scattergrams geared toward under correction in the higher corrections. We

did it intentionally knowing that yes, that is going to compromise efficacy but frankly just reality, nothing about this Panel or this process we weren't doing this to obtain FDA safety and efficacy. We were doing this to study and validate LASIK. So, as a group when we came together our goal was not to shoot for 100 percent efficacy which we could have done by overcorrecting everyone by 1/2 diopter and we would have great vision, but we would have terribly unhappy patients. We did it for long-term benefit of the patients and the long-term validation of LASIK and the nomogram still intentionally under corrects people understanding that reoperations are a fundamental part of the procedure and as we showed reoperations can be performed safely. So, that is how I would answer your question. I don't know that it is fair to look at efficacy that falls off at 14 diopters because you are trying to under correct as being an absolute criticism against this.

DR. MC CULLEY: What were final results after retreatment in that group?

DR. KEZIRIAN: We improved the uncorrected visual acuity in the retreated group. We had --

DR. MC CULLEY: In the higher range?

DR. KEZIRIAN: In the higher range we had, I am sorry, I want to give you the exact number. The uncorrected

visual acuity pre-enhancement 20/40 or better went from 43 percent in the pre-reoperation to 98 percent in the post-reoperation. Efficacy was good. So, I just think that we have to consider this thing in the context of how it is being offered and how it is being practiced and because we are trying to certainly barter some efficacy in order to gain safety, I don't think that that is necessarily a negative thing about the way the study was done or that LASIK is performed.

DR. MC CULLEY: Dr. Wang?

DR. WANG: I just want to clarify my question. I think in addition to safety and efficacy there is a basic question of confidence in the data irrespective of what the merit or what is the point we are trying to show using the data, and since we are talking about very high percentage success and very low percentage of failures and if you only have three patients the relative error of one patient may have probable 30 percent. So, I am trying to get a sense where is the -- obviously minus 7 has good statistics. Minus 13 is terrible. Where do I --

DR. KEZIRIAN: Why is it terrible?

DR. WANG: Because of the sample size. So, somewhere along the line let us say minus 11 where we can say that gives us a reasonable statistic in terms of error

is comparable to what we are talking about in terms of safety and efficacy and so, at a range lower than that we can draw conclusions more confidently. At a range higher than that we have to use more intuition and others because we cannot rely on these percentages anymore. The statistics itself is of little significance at the threshold.

DR. KEZIRIAN: I agree with you and have the same feeling about wanting to have huge numbers. I agree with you, and I think Dr. Casebeer has a comment he wants to make as well but my reaction to that as a statistician is that our distribution in the higher ranges actually far exceeded by multiples what the natural distribution of higher refractive errors are in the population, and so, I think that our data do adequately reflect what would be encountered in practice and I think they do adequately reflect what exists.

So, while I would like to have each bin chock full, that will never happen no matter how long we wait. Those patients just aren't out there in enough numbers. It is important to give them information about safety.

It is important to give them information about efficacy, and it is important to prevent those patients from being treated with double carding and other innovations which would be required should they not have access to the

technology because they are going to be treated. I think Dr. Casebeer had a comment to make about the patient satisfaction.

DR. CASEBEER: No, it is really the same thing. I don't know how you could ever study in large numbers anything that has an occurrence in the population of 1 or 1-1/2 or 1/2 percent. I don't think it is possible, and I think since the patients are satisfied in the patient questionnaire that probably it is an inherent problem with a study like this where there is a big drop off, but I agree with Dr. Kezirian otherwise.

DR. MC CULLEY: We have addressed the issue before in the Panel of this inability to get large numbers in high ranges of myopia and in the higher ranges of astigmatism, and we have accepted lower numbers in the past weighing again the real world and the benefit, potential benefit to the patients and their options or alternatives. So, we have addressed this before, and I think dealt with smaller numbers than these more commonly encountered situations.

Dr. Pulido?

DR. PULIDO: I really would like your help because if I can get over this accountability problem this accountability hurdle, I would be very happy in accepting and approving this FDA submission, but here is my conundrum.

If we go to Page 196 of Volume 1, our 3-month accountability range is from 0 percent in at least two cases in two centers to 100 percent. Okay, your argument thus far is that those people that didn't come back it was because they were so happy they didn't come back. So, just taking a polarity then if that is true through all centers then if some centers had no patients coming back and therefore they were all very happy, then the ones that had 100 percent return, they were all unhappy, and is that how we should interpret the findings, that the more accountability there was the more unhappy these patients were? I am just using the flip of the argument that you are using.

DR. KEZIRIAN: Okay, as I pointed out, the points that you have brought up are, I think largely done away with, with the observation that we did provide a last visit carried forward analysis, Table 8 for eyes that missed visits in both cohorts, and they don't differ from the rest of the group. FDA looked at it. We looked at it, and you know, the people have asked, "Show us the data on the eyes that don't come back." We have done that, and it is in the application, and they don't differ widely. So, you know, we have only conjectured that it is more difficult to get the satisfied young active patient back into the practice. Clearly some of our investigators had more sway with their

patients or more commitment to the study and were able to get them in. I don't know that that so much parallels the patient satisfaction as the effectiveness of that investigator's commitment to the study to get the patients in. The two centers that had zero, the one with the large number of eyes had a change of doctor. The doctor was no longer at the clinic, and they couldn't participate. In fact, they withdrew from the study, but because the patients were enrolled they were submitted but actually that center is not an active center in the study.

So, that center was effectively removed because the doctor no longer was at the clinic to follow the patients. So, that looks terrible to have a zero follow-up, but the zero follow-up was there because the doctor was no longer there.

So, when we look at those things and at Dr. Ferris' question the answer is that the exclusion was randomized before we looked at the results. We did look at the N because we wanted to have the 90 percent level at 3 months, and we set it at 80 percent because it so happens that 80 and 100 average out to 90 and it gave us the answer that we are looking at, but it was done before we ever looked at the results, and in fact, at times we have regretted that because some of the other results were

better, and it was a randomized thing, and it was preset. It was preset to come up with the 90 percent.

The other thing is that because we provided that last visit analysis we feel that some of the anxiety is misplaced because we did give you those results and they are there, and they are fine, and having done that we feel like we have satisfied our obligation to integrity to give you everything.

We aren't giving you 57 percent of the applications. We are giving you 100 percent of the applications. We consider them both from safety and efficacy. We have given you safety and efficacy on both, but when we know that issues like stability want to be evaluated against the cohort with good follow-up and other efficacy issues want to be evaluated against a cohort with good follow-up we broke down the cohort that had good follow-up so that we could do that, but we did provide all results for all eyes.

DR. MC CULLEY: That is not the issue. The issue what you weren't able to provide that wasn't there, I think, just very simply put. It is not a question of you massaging what you have.

DR. KEZIRIAN: Right, well, that wasn't the question.

DR. MC CULLEY: It is the fact that you don't have the follow-up on some that is the concern. It is not an integrity issue, nothing of that. I have heard no sense of that. It is that you have a bunch of patients who didn't come back.

It is as simple as that.

Dr. Sugar?

DR. SUGAR: A corollary question then, when we discussed earlier if we could make a recommendation that you get more data, is that a realistic thing from your standpoint? Have you pushed as hard as you can to get the patients that you want to get and if we made a requirement for a follow-up, I guess, requirement for approval that you get more patients, do you think you realistically could do that?

DR. MC CULLEY: Let me ask for just a point of order here? It is a good question. I am not sure it is one that is appropriate for us to ask sponsor to respond to where it would affect, I am not certain, okay? I don't want to get in trouble in later.

PARTICIPANT: It is quite appropriate to ask the sponsor whether or not they feel they can get the information that you feel might be required to make a decision.

DR. MC CULLEY: Please answer the question.

DR. CASEBEER: Let me comment on that? We don't like that any better than you do, obviously, and we did monumental things in terms of Fed Ex packages, certified letters, phone calls, faxes, any type of communication already to try to solve this problem because clearly we wanted it solved, and I think we have extracted what we can out of the investigators and a future effort would not reveal very much because we have been very, very difficult to the point of myself threatening people to be out of the study if we didn't get what we wanted.

DR. SUGAR: You are talking about pursuing the surgeon or pursuing the patient?

DR. CASEBEER: We are talking about pursuing in most cases the surgeon.

DR. MC CULLEY: He is saying that he doesn't think it would yield much. That does not preclude us from having that as a condition though. It doesn't mean we put it in. It doesn't mean we have to take it out.

Dr. Wang?

DR. WANG: I just want to follow-up on the question that Dr. Pulido just raised 10 minutes ago or so. Just along the lines of thinking of this process and trying to resolve this issue from our intuition and clinical

experience my personal clinical experience is that it tends to be in terms of direction of whether those patients who failed to show up they tend to do better or worse. Just from personal experience they tend to do better. Usually and particularly in LASIK in this particular type procedure if they have problems they tend to come back. So, I guess that sort of relieves some of your anxiety maybe to some extent.

DR. MC CULLEY: Dr. Bullimore?

DR. BULLIMORE: Just an observation. I mean this one clinic where there were 179 patients enrolled and nobody was followed up to any extent, you have my sympathies and what would have been useful for me in my review and my comments would have been had you emphasized the fact that the doctor had left the office and basically that clinic site had to be closed down. If you had made that more clear in your application I would have -- you would have had more sympathy up front. You basically with that one individual's behavior, whether intentional or whatever, you were concerned about 86 percent. Your ceiling was set at 86 percent. So, in terms of guidelines you had a big hole in your ship right there. I am prepared to put this issue to bed and let us move on.

DR. MC CULLEY: Dr. Rosenthal?

DR. ROSENTHAL: I just want to remind the Panel that in the past they have required additional information from another PMA holder which the agency then sought to obtain and in fact was brought back to you and in another instance, two instances you actually have requested as part of the conditions of approval general information.

DR. MC CULLEY: So, that is an option available to us when we bring our wisdom to words.

Dr. Macsai?

DR. MACSAI: Though I think we are not finished with the accountability issue I have just a few questions for the sponsor, and I assume this is the time to ask them. Regarding the nomograms you stated in your presentation that a paper was published in the Journal of Op Tech Cat Refractive Surgery, and I am not familiar with that journal. Could you tell me is that --

DR. KEZIRIAN: It is a Williams and Wilkens publication out of Philadelphia. It was begun about a year ago, and I don't know how successful it has been, but the paper was included in the application.

DR. MACSAI: But it wasn't in the bibliography, and that is why I was confused.

PARTICIPANT: The paper is in there.

DR. MACSAI: Okay. Did you, you said you looked

at a lot of different identifying factors, sex, etc., did you look at age stratified by sex to see if there was a difference in outcome and did you, also, look at women on hormone replacement therapy?

DR. KEZIRIAN: We looked at all the factors you mentioned including age. In fact, a nomogram that we did find a significant correlation with age and used age and pre-operative refractive error to formulate the actual nomograms. We did not find a sex differentiation on a statistical basis. We did not consider hormonal therapy versus none in that analysis.

DR. MACSAI: Another question I have is in your presentation, Dr. Kezirian you talked about the stability with your paired analysis which was a very nice presentation. What overall percentage of patients did that represent?

DR. KEZIRIAN: About 35 that came in for the visits to be able to analyze it.

DR. MACSAI: Also, in your presentation you had a, you walked us through your graphs, your bar graphs for patient symptoms including glare, halos and visual fluctuation and Dr. Mannis did some quick math noting 20 percent of patients complained of worsening of glare and is it statistically fair to summarize those numbers because if

it is then I, also, would add that I calculated that 26 percent of the patients were complaining of halos on the worst side and 26 were complaining of visual fluctuations?

DR. KEZIRIAN: Right, you just brought up the point I think that is really important and that is that this is a change pre-op to post-op So, it is not an absolute do you have halos. It is do you have halos pre-op and do you have halos post-op and comparing your two scores. If you get better you fall on the better side and if you get worse you fall on the worse side and that was the way this was structured.

We find, I don't know about the math. I think you might have been looking at the wrong side of the chart. There were 5 percent of the eyes that were worse more than, 3 points or more.

DR. MACSAI: No, all points is what I am asking, not 3 points or more.

DR. KEZIRIAN: Right, there were 15 percent that were worse 3 points and so that adds up to 18. Fifty percent were no change, and the rest were better which was about over 30 percent. So, you know, the shake-out between minus 1 and plus 1 is questionable statistically because of the way that the questionnaire was administered. They had no number clue. They just made an X on a bar and we graded

it afterwards with numbers. So, if you look at that there was some worsening, but if you consider that moving a point or two may not be as significant as moving 5 points the number that really became worse in glare was very small.

Now, I am sorry?

DR. MACSAI: Did you validate your questionnaire to determine if a movement of 1 point was significant?

DR. KEZIRIAN: We did not perform a statistical analysis asking that question, no, whether or not 1 point was significant. We could, but it would all be, you know, frankly, it would be conjecture.

The other question you asked was about halos.

DR. MACSAI: Halos and visual fluctuation. You presented three different slides.

DR. KEZIRIAN: Right, and because we had a mean that didn't change, a T test that showed no statistical significance in the before and after answers and a distribution that was gaussian we just interpret that as meaning there is not a significant measurable effect of this procedure on those symptoms.

DR. MACSAI: But if you add all the numbers on the worse side, when I added them is it fair to say that 26 percent complained of worsening of halos whether it be mild, moderate or severe?

DR. KEZIRIAN: That is a true statement. Yes, it is. That is a true statement and it would be balanced by the same if that many get better. Why? I didn't find out.

DR. MACSAI: I didn't ask you why.

The other question I have is you talked about re-operations and the effect on uncorrected visual acuity which was very impressive and I was wondering how far out you had followed those patients. Was that effect at 1, 3, 6 months after --

DR. KEZIRIAN: For that analysis we used the last visit analysis. We looked at the last time they had come in. For some patients that was as short as a month and for some of them it was as long as almost a year. We used the last visit analysis on that.

DR. MC CULLEY: I have three people I know that are queued up. Rick, you were first, then Eve, then Janice.

DR. FERRIS: My comment actually goes back a long time ago to what Ming was asking about with regard to the ability to look at the higher levels of myopia and make some determination as to whether they should be included or excluded. I am sure if you did the math to say what power you had to show that this, what you observed there was the same as at the less than 7 level of myopia you could get a number that would tell you you don't have very good power to

say that at least within a narrow confidence interval that they are the same.

On the other hand, it seems to me that this is what Dr. McCulley was talking about earlier that to some degree we are going to have to use some clinical judgment because this kind of generalizability problem extends in any study. If you start looking at minority populations within the study, minorities in any way that you are talking about it, your power to say that the treatment effect in that subgroup is the same as the overall treatment effect is inevitably killed by the sample size. So, you have to look within there to see if there are any clues for differences, and I think you addressed that point fairly well with regard to where the differences occurred and how we might address that.

Now, in the end we are lacking data. So, we are going to have to make a clinical judgment. The second question has to do with the issue of the missing people that we have been perseverating about, the ones that you don't have information on and we understand that that is a particular problem when people aren't sick. These people don't have any good reason to come back necessarily and the question is whether you had ever tried administering the questionnaire, for example, over the phone or because I

suspect that the people that came to the podium earlier today would have no problem answering that questionnaire over the phone as to how they liked this procedure. I haven't given them the questionnaire, but I can predict what their response might be, and the issue here is whether the people that you don't have follow-up on have similar responses to the questionnaire as the people that you do have follow-up on making you believe that the cohort that you are missing data on is similar to the ones that you have data on and making it more easy to swallow the idea that you are not missing some terrible bit of information that is lurking out there that we just don't know about.

DR. MC CULLEY: Questions for the sponsor continue. Dr. Higginbotham?

DR. FERRIS: Can I get a response to that or not.

DR. MC CULLEY: What was the question?

DR. FERRIS: The question is whether they have thought about doing a questionnaire over the phone.

DR. MACSAI: Which was my first question.

DR. KEZIRIAN: For a variety of reasons we haven't and resources clearly is one of them but it is my understanding that that has been done with some of the manufacturer's studies and it is my understanding that in those manufacturer's studies specifically with this laser

with VISX that when that was done the mean responses mirrored or were better than what was actually done, and I think that to a certain extent these are the same people we are surveying again, but the only way I can respond and answer is we haven't done it.

DR. MC CULLEY: If appropriate at the appropriate time, would we want to make that as a condition?

Dr. Higginbotham?

DR. HIGGINBOTHAM: Yes, thanks for asking my first question, Dr. Ferris. My second question relates to the comment we heard earlier today that there was a poor success rate in the combined centers for the higher myops and that was thought to be related to learning curve but as I look at some of the clinics and the remainder cohort I see there are as many as 139 patients and one of these, I mean this doesn't sound as if it is an inexperienced surgeon necessarily and my question therefore is whether or not this is probably not necessarily learning curve but related to the fact that these are higher myops and there is a greater risk that you are going to have some difficulty in meeting your goals.

DR. KEZIRIAN: The pooling analysis I generally would agree with your comment except that the experience wasn't lower, I don't think in any of the clinics. I think

it was pretty even across the board, and I think that that conjecture was made by the statistician who did, I think, a wonderful job looking at it but didn't know the clinics and just conjectured that, and it was plausible, but I don't think it was accurate.

Your comment about risk, I would simply say that the outcomes that we compared for poolability were efficacy outcomes, and it wasn't for best acuity. So, I don't know that that would be presumably could risk, just success. The success rate was lower. I am not sure the risk rate was higher.

DR. HIGGINBOTHAM; Okay, I accept that amendment but it is probably related, therefore, to the high refractive error.

DR. KEZIRIAN: Right, and therefore we agree.

DR. HIGGINBOTHAM: Yes, thank you.

DR. MC CULLEY: Dr. Jurkus?

DR. JURKUS: Going back to the patient survey could you please tell me when that was given to the patients, at what visit?

DR. KEZIRIAN: Yes, it was provided pre-operatively and at the 3-month follow-up visit.

DR. JURKUS: Then as the second question on that the people that reported a change for the worse in terms of

halos and vision fluctuation and glare, was there any breakdown between the higher, greater than 7 diopters surgery and the less than 7 diopters surgery?

DR. KEZIRIAN: Not that we provided in the analysis. We have done that informally but not in exactly the same data set. It appears that there is a little bit more in the higher group.

DR. MC CULLEY: I don't think that we should be working under the false assumption that the higher ranges do as well as the lower ranges.

DR. FERRIS: Of course not.

DR. KEZIRIAN: They don't.

DR. MC CULLEY: They are gaining more in refractive error, but they do not -- it is not, they do not do as well in whatever analysis one wants to apply.

DR. FERRIS: How about are they happier?

DR. MC CULLEY: That would come in in the patient survey. Are they happier or --

DR. FERRIS: I mean they might be.

DR. MC CULLEY: They are gaining more, but they are risking more. They are not going to do in general as well by most measures, but you have an indication of -- and they are in the range as best we can tell of acceptability, but in terms of satisfaction are they happier or unhappier?

DR. KEZIRIAN: We found that the higher patients tended to answer happier than the patients in the midrange and the patients in the low range tended to answer happier than patients in the midrange.

DR. MC CULLEY: Who was the happiest, high or low?

DR. KEZIRIAN: The high.

DR. MC CULLEY: So, high, low, intermediate?

DR. KEZIRIAN: Exactly.

DR. MC CULLEY: Dr. Wang and again, these are questions to sponsor. So, questions to sponsor and then we need to allow sponsor to retire from the table.

Dr. Wang?

DR. WANG: Ming Wang. I have a question about visual quality, and this will pertain to the labeling later to be discussed. Specifically regarding halo, we know that clinically the halo experience after LASIK tends to be more visually significant and affecting the quality of vision than halos that occur naturally in patients without ever having surgery. From a physics standpoint we know that has some rationale if the pre-op the halo come from asphericity of corneal lens combined optics where post-op comes from this artificial excavation of cornea just like volcano on surface of the cornea, but off sharply at 6 millimeters. Have you attempted to assess the degree of halo because from

my clinical experience those halos that occur after LASIK tend to be more significant?

In other words if you just assess whether you have halo better or worse pre- and post-op you may not address a more important hidden question that is the degree of halo which may more potentially reverse their post-LASIK visual quality compared with naturally occurring mild halo pre-op without surgery.

DR. CASEBEER: The only way that I think you could have a judgment about that is it would seem like people who said that they had one for halos pre-op and they thought it was really worse or really different they would grade it higher in the other, and it would show up to the left side on that bell curve, but we didn't exactly say, "Is this halo better than that halo?"

DR. MC CULLEY: Dr. Bullimore?

DR. BULLIMORE: A couple of very quick questions while he is still at the table. Firstly, do you think pupil size is an important factor in patient satisfaction with this procedure?

DR. CASEBEER: As a personal matter, I mean do I, personally, think that?

DR. MC CULLEY: No, I don't think we want personal

--

DR. BULLIMORE: Does the sponsor believe that pupil size is an important determinant in -- okay.

DR. CASEBEER: I want to answer, but it doesn't seem appropriate.

DR. MC CULLEY: No, I think you told us before you did not assess pupil size.

DR. CASEBEER: Correct. So, we have no opinion.

DR. KEZIRIAN: So, we don't have a company opinion if you would. It would only be personal.

DR. BULLIMORE: That is fine. The other issue was in terms of the indications for the device do the numbers you give there refer to spherical equivalent or sphere?

DR. KEZIRIAN: Say the question again?

DR. BULLIMORE: In your indications for, your proposed indications for the procedure you are asking for up to minus 14. Is that spherical equivalent or sphere?

DR. KEZIRIAN: Sphere.

DR. BULLIMORE: Is that minus cylinder form or plus cylinder form?

DR. KEZIRIAN: Minus cylinder form.

DR. MC CULLEY: Dr. Pulido?

DR. PULIDO: Proceeding with what Dr. Ferris said you said that trying to get 100 percent follow-up on this by phone on this remainder cohort would be almost

insurmountable. What about randomly selecting 20 percent and making sure that what you suspected was that they are doing very well is truly the case? Would you still feel that that is insurmountable?

PARTICIPANT: That is not appropriate.

DR. MC CULLEY: I don't think we care whether they do if we think that is appropriate. It may be a very good suggestion, but whether they think that they can do it or not or it is appropriate on their part is not relevant. We decide.

Mr. Macsai?

DR. MACSAI: We discussed that you had different shapers but that this data is all with one shaper. Is that correct?

DR. CASEBEER: That is correct.

DR. MACSAI: That is the diameter of the flap that the shaper in this study lifts?

DR. CASEBEER: It is keratometry dependent with steeper corneas giving larger caps. Probably with the Chiron ACS at around 43 or 44 diopters a 8.4 or 8.5 millimeters, someplace around in there. We do have other keratomes in the study but they are not in this database. They are at another time, and we are not asking clearly for some kind of an approval for the Chiron ACS. It just happens to be --

DR. MC CULLEY: We got that well clarified before.

DR. MACSAI: One other point, one last point of clarification. You said, "Minus 14 sphere and 6 diopters of cylinder and minus cylinder." Do you mean minus 14, minus 6 at say 90 or 180? What indications are you asking for? Because I was equally confused as Dr. Bullimore.

DR. CASEBEER: It is in two different parts really, sphere and cylinder, so that theoretically that could occur, minus 14, minus --

DR. MACSAI: Because that is the spherical equivalent of minus 17.

DR. CASEBEER: Yes, certainly it is, ma'am.

DR. BULLIMORE: But you don't have any patients in that range to present to us.

PARTICIPANT: It seems to me if I can make this statement more of a labeling issue than anything. I mean there have been warnings suggested and everything else about higher ranges, and I think that the hazard is in requiring the only alternative for treatment of such eyes to be individual innovations such as double carding. I think it is very hazardous.

Okay, questions to sponsor, sponsor only answers to questions. No editorial comments, sorry.

If there are burning questions for sponsor still,

please so indicate? Dr. Matoba, did you have one or yours isn't burning.

DR. MATOBA: It is labeling.

DR. MC CULLEY: I see no further questions for sponsor. We will ask sponsor to depart the table. We thank you for your responses.

Okay, Bernie you need to get your questions ready to give to us. Are there any other comments, questions statements, whatever variations on the English language that we need to do before we put the questions up to respond to?

Dr. Matoba?

DR. MATOBA: Alice Matoba. Just a comment about the labeling. In their study the exclusion criteria included active ocular disease, anterior signal pathology and also, any type of intraocular surgery but in their proposed labeling that is not -- previous intraocular surgery is not mentioned either as a potential contraindication or as a caution that efficacy has not been proven for those patients, and I think that the labeling should be consistent with what they use as exclusion criteria in their study.

DR. MC CULLEY: Good point. Thank you. Any other comments?

I think what we will do now is Bernie will present

his questions to us one at a time. Dr. Bullimore is going to scribe as we raise issues and be sure you have Dr. Matoba's issue that we will bring up again as well.

DR. LEPRI: Mr. Chairman, there is one point I would like to address one of the questions regarding the labeling in pupil size. The current VISX labeling states that astigmatic patients between the ages of 21 and 30 should be reminded that due to their larger pupils they are more likely than the over 30-year-old population to experience a degradation in visual performance under these conditions.

DR. MC CULLEY: Do the Panel agree with accepting that as an addition to the labeling.

PARTICIPANT: It is already in the labeling.

DR. MC CULLEY: But we are going to have separate labeling for this so as to carry forward and not have lost - - it is an operational point that the FDA can probably figure out, but we don't want that lost I don't think.

DR. BULLIMORE: Correct, we want to add it for the spheres.

DR. MC CULLEY: So, you have that appropriately indicated?

DR. LEPRI: No, that is not the problem. There is a computer problem. That is the screen.

DR. BULLIMORE: If it pleases the Chair, why don't I read the first question while Dr. Lepri is recovering his computer?

DR. MC CULLEY: Good.

DR. BULLIMORE: Do the clinical data in this PMA provide sufficient follow-up on the stability of the safety and efficacy of LASIK for the correction of myopia with or without astigmatism in the ranges indicated?

DR. MC CULLEY: Okay, I think we have, there have been stated issues. Let us do sphere initially. What range is the Panel comfortable with --

DR. BULLIMORE: This is the --

DR. MC CULLEY: Oh, follow-up, accountability, okay, sorry. I fixated on the word "range." Accountability. Would you like to make a recommendation, Dr. Mannis or respond to that question initially, take the first shot at it?

DR. MANNIS: I must say that I am, Mark Mannis, I am waffling a bit. When I came to the meeting I didn't feel as uncertain about the missing 43 percent as it were as I do now, and I would like to recommend that the obstacles notwithstanding that the sponsor turn back to its cohort and try to provide us with additional follow-up data.

DR. MC CULLEY: Dr. Pulido had a specific

recommendation. Let me ask him to state that and see if there is Panel concurrence with that?

Dr. Pulido?

DR. PULIDO: Proceeding from what Rick Ferris had said my suggestion had been to randomly select 20 percent of that remainder cohort and calling those patients and seeing how truly satisfied they had been and using just that 20 percent of the remainder cohort.

DR. MANNIS: Mark Mannis, but you are talking only about a satisfaction survey. I am actually talking about measuring objective parameters, visual acuity.

DR. PULIDO: I would be happy with just a satisfaction survey.

DR. MC CULLEY: Dr. Rosenthal?

DR. ROSENTHAL: Twenty percent of those whom they have no data on?

DR. PULIDO: Correct.

DR. MC CULLEY: Then what percentage of that percent do they have to get responses from? We have requested in the past that sponsor by whatever mechanism gets whatever information sponsor can get by whatever means, always legal, to get a response, and I don't recall how we worded that before, but I think something along those lines seems to be, I hear from just trying to interpret all of the

various things that have been said that that is the compromise that the Panel would be most comfortable with and the question is how are we going to state that, that the majority of the Panel will be most comfortable with, and the question is how to state that.

Dr. Ferris?

DR. FERRIS: Rick Ferris. I am not going to suggest how to state it but I had a question with regard to, that relates to whether this is sufficient information or not, and it has to do with my concern of is this sufficient information; does it stand alone to justify approving this PMA or not, and as an alternative, and I don't know whether it is possible, so I am raising this as a question, it might be that to say that this is equivalent to an already approved procedure is different than saying that on its own it stands alone, and I don't know whether that is an option for us to say that this is -- I see some shaking heads like it is not an option.

DR. MC CULLEY: I don't think we can go the substantial equivalence route. If they could we probably wouldn't be here.

DR. FERRIS: I withdraw the suggestion.

DR. MC CULLEY: Dr. Morris?

DR. MORRIS: This may be a really elementary

question, but I thought I heard the sponsor say that they used every human possible means to get feedback from these patients, and --

DR. MC CULLEY: They said that they worked principally with the physicians. They didn't go directly to patients.

DR. MORRIS: Right. So, are you suggesting that the sponsor now go directly to the patients around the surgeons?

DR. MC CULLEY: As a possibility. I am not trying to suggest anything. What will make the Panel comfortable?

DR. MORRIS: That doesn't make me comfortable. I mean I am taking their word for what they said. They said that it was impossible to get this feedback, and now to force them to go back and get feedback so that we feel better about it doesn't make me feel better.

DR. MC CULLEY: Is this an attempt to feel good and just a smokescreen or is it real, and I don't know.

Dr. Macsai?

DR. MACSAI: I think the impossible has been done before, and I don't think that the Panel ever has intended to do any sort of smokescreen nor has any sponsor. I mean it is just a matter of establishing safety and efficacy with acceptable accountability. That is all.

DR. MC CULLEY: Okay, Dr. Higginbotham?

DR. HIGGINBOTHAM: I guess my greatest concern rests with those clinics that have 0 percent follow-up at 3 months, and perhaps one could do a more targeted questionnaire or survey of those patients by phone just to get a sense of their level of satisfaction and perhaps 20 percent of the cohort of those centers might be a reasonable compromise to get us off this issue.

DR. MC CULLEY: So, 0 to 20 is really going to answer the issue?

DR. HIGGINBOTHAM: Well, no, at least to sample those patients, at least a reasonable sample of patients that at least three of the centers that have more than two patients enrolled in the study.

DR. MC CULLEY: It seems to me crudely put those are bad actors, those centers. They weren't responsible investigators for whatever reasons.

DR. MACSAI: Historically I think this is not under the Panel's purview. If the Panel feels that the accountability is inadequate, then we either decide if this PMA is acceptable or approvable, approvable with conditions or not approvable.

DR. MC CULLEY: Okay.

DR. MACSAI: And then we set what accountability

we feel is appropriate and how a sponsor meets it is under a sponsor's purview and it is inappropriate for us to dictate.

DR. MC CULLEY: It is not necessarily inappropriate. I mean we can dictate things that we would want them to do. I mean basically what you have done is called the question on this issue, and I am going to ask for a vote on that, but Dr. Bullimore's hand got up before I said that.

DR. BULLIMORE: I am happy just to vote.

DR. MC CULLEY: All right. So, the question is that we are going to vote on is do the clinical data in this PMA provide sufficient follow-up, and I think it was changed a little bit, of the follow-up of the LASIK for the correction of myopia with and without astigmatism in the ranges indicated for voting members of the Panel, and there are 11. I know it is not a formal vote, but it is a consensus vote at this time, but I would like to take that straw vote as to the answer to the question.

DR. MANNIS: This is conditions or without conditions.

DR. MC CULLEY: It can be yes. It can be yes, with conditions. It can be no, I suppose. This is a tough one to get over.

DR. ROSENTHAL: This is Dr. Rosenthal. You

obviously have an issue with accountability.

DR. MC CULLEY: That you is the plural.

DR. ROSENTHAL: I mean you, plural, many of you and when you make your final recommendations you can recommend how you feel that should be altered, as you have done so in the past.

DR. MC CULLEY: Okay, ordinarily what we do is answer the questions as we go. I am trying to figure out how we can answer this question.

DR. ROSENTHAL: I think the agency understands that you have a problem, you, collectively have a problem and that we will wait until the end of the questions and the final decision to --

DR. MC CULLEY: So, the Panel is uncertain as to how to answer this question at this point.

Let us go to the next question.

Yes?

DR. YAROSS: Mr. Chairman, I would just propose that you ask it in terms of the data in front of the Panel today.

DR. MC CULLEY: That really is what the question is. I mean that clarifies the question. I don't think that is going to help the Panel answer it.

Okay, is there a sense for a straw vote?

Do the data in the PMA provide sufficient follow-up of LASIK for the correction of myopia with and without astigmatism in the ranges indicated in the opinion of the individual Panel members?

DR. FERRIS: A point of clarification. This is Rick Ferris. That is by itself, not using other clinical information?

DR. MC CULLEY: No, this is not in isolation. This is given all information that each of us brings to the table, the data, our interpretation of the data, our knowledge base, our sense, what is the individual --

DR. ROSENTHAL: Sorry, Dr. McCulley, this is Dr. Rosenthal. I think actually Dr. Ferris is more correct. It is does the data that the sponsor has presented in support of their application provide sufficient patient follow-up.

DR. MC CULLEY: All right, okay, but our assessment --

DR. ROSENTHAL: And I think we have gotten the sense that the Panel has.

DR. MC CULLEY: All right. So, what --

DR. ROSENTHAL: I don't know if you need a straw vote.

DR. MC CULLEY: Okay, so just for data as presented does the Panel feel like there is sufficient

follow-up for the correction of myopia with or without astigmatism in the ranges indicated?

All of those that think that it is, raise your hands?

(There were two hands.)

DR. MC CULLEY: All of those that do not, raise your hands?

(There were six hands.)

DR. MC CULLEY: Okay, the majority think that it is not.

Okay, go to the second question. Would you like to read the question for us?

DR. LEPRI: What are the Panel's recommendations regarding the sponsor's presentation of stability data for LASIK and --

DR. LEPRI; Excuse me for interrupting, Dr. Rosenthal. There was another part of that question, and I am sorry, part of it is my fault for not having emphasized it, and that is is the 6-month follow-up assuming they had not 100 percent at 6 months, are you happy with the 6-month data because are retreating slightly from previous decisions where sometimes 6-month data was, you wanted something beyond 6-month data.

DR. MC CULLEY: We have wanted 2-and-3-month data.

PARTICIPANT: In the guidance document it is 1 year, 90 percent at 1 year. I mean is that what you are getting at?

DR. MC CULLEY: No, that has been clarified at another meeting before. I thought the same thing, but the way it reads and it was Morris that corrected it, it was that stability at two points 3 months apart.

DR. BULLIMORE: I think what we are saying is have they demonstrated, assuming that they had all the accountability issues intact, have they demonstrated that 6 months is all they need.

DR. MC CULLEY: For stability?

DR. BULLIMORE: No, for everything? Are you willing to accept the data at 6 months?

DR. MC CULLEY: At their level of accountability?

DR. BULLIMORE: No.

PARTICIPANT: If the accountability was perfect would 6 months be enough follow-up?

DR. MC CULLEY: Okay, so this is a theoretical question in a sense.

DR. BULLIMORE: Yes, follow-up could be follow-up in terms of accountability and it could be follow-up in terms of time, duration and so I just want both of your inputs on that.

DR. MC CULLEY: As far as accountability that is what we --

DR. BULLIMORE: We have gotten that input. Now, -
-

DR. MC CULLEY: Minimum follow-up time with good accountability at that time point, what is that time point set at?

DR. BULLIMORE: Yes, for what procedure?

DR. MC CULLEY: For this particular PMA?

DR. BULLIMORE: Yes.

DR. MC CULLEY: Relative to stability or all data?

DR. BULLIMORE: All data.

DR. MC CULLEY: All data.

DR. BULLIMORE: I mean the stability data are the data upon which we base the duration of the study.

DR. MC CULLEY: But once you have stability then the other data is useful.

DR. BULLIMORE: Is used to ensure that the safety and efficacy is supported.

DR. MC CULLEY: To me the absolute time is a float depending on other data, but, okay, Mark, you are frustrated.

DR. BULLIMORE: I am frustrated. I am unclear whether the FDA is asking us to vote on this particular PMA

or whether they are asking us to make recommendation for the future. I am confused.

DR. YAROSS: May I try restating it? This is Marcia Yaross. I think the question was if you had this data set with 90 plus percent accountability would you feel that you had sufficient follow-up in terms of time?

DR. MANNIS: Is 6 months enough is the question.

DR. MC CULLEY: At 6 months. You didn't give a number, but at 6 months.

DR. YAROSS: With the 6-month data set you have if the accountability --

DR. MC CULLEY: If we had 90 percent accountability at 6 months would we feel that this data was acceptable data in the --

DR. YAROSS: To determine refractive stability.

DR. MC CULLEY: No, he said, "Everything."

DR. YAROSS: To determine safety and effectiveness given that the data came out the same out as they were but you had accountability that satisfied you, is that the question?

DR. FERRIS: And I take it this is an issue because the guidance suggests 1 year. Is that right?

DR. ROSENTHAL: It is an issue because the sponsor has come in with 6-month data and I think if they have

difficulty getting information up until 6 months I want to be sure that the Panel is happy that they will accept the 6-month data set. That is really what I am asking.

DR. MC CULLEY: I think it would depend, I mean we can look at the 6-month data set. Whether it is acceptable or not depends on what the data is.

DR. ROSENTHAL: You have been given the 6-month data set. So, I am asking you --

DR. MC CULLEY: If the accountability --

DR. ROSENTHAL: Obviously the accountability alters your decision, but --

DR. MC CULLEY: Okay, what you want us to answer for you is if there were acceptable accountability in this particular PMA at 6 months would this data be acceptable to us?

DR. ROSENTHAL: Correct.

DR. MC CULLEY: All of those that it would be acceptable raise your hands?

(There was a show of hands.)

DR. MC CULLEY: All of those that it would not be raise your hands?

(There was a show of hands.)

DR. ROSENTHAL: Thank you, Mr. Chairman. I am sorry to have been confusing. It was my fault in writing the

question.

DR. MC CULLEY: I was confused. I am glad you are accepting the responsibility.

Okay, next question, Question 2.

DR. LEPRI: What are the Panel's recommendations regarding the sponsor's presentation of stability data for LASIK in the refractive ranges indicated in this PMA?

DR. MC CULLEY: Dr. Bullimore?

DR. BULLIMORE: Would you entertain a motion or an informal motion?

DR. MC CULLEY: How about a suggested --

DR. BULLIMORE: Basically that we accept these data, but I would like to see in the conditions some wording be included in the labeling about stability being poorer in the higher refractive ranges.

DR. MC CULLEY: How would you specifically state that?

DR. BULLIMORE: Refractive stability may be poorer above minus 7 diopters of correction.

DR. MC CULLEY: Is there agreement?

DR. MACSAI: Can I make a friendly amendment that refractive stability was only studied up to 6 months post-op.

DR. BULLIMORE: I accept the friendly amendment.

DR. VAN METER: I have several things to bring up about the higher refractive ranges. We have seen less efficacy. We have seen less safety in the efficacy issue that is at 79 percent 20/40 versus 94 percent 20/40. When we set up the original guidance documents it was really with the specter of PRK on the horizon, and I think most surgeons think that LASIK is better than PRK for a number of reasons. Yet the bar has not been raised any. So, looking just at the subset of the greater than minus 7 we see less efficacy and less safety both of which are below the guidance document even though the bar has not been raised. In addition there are other treatment modalities out there even outside of spectacles to correct these patients and this doesn't mean that they cannot have LASIK, but I am not sure that we should approve the higher range based on the information that we have now.

We can get around this with appropriate informed consent.

DR. MC CULLEY: What we decided before when we discussed whether to add specifics to the guidance document for the higher ranges is that we would not try to create artificial numbers but take into consideration our realization and the reality that those patients typically do less well, and we would make a judgment as to what the

performance was whether it was acceptable or not.

So, we left it soft so that we would bring judgment to it and did not change the guidance but with the understanding that those patients would typically not respond as well as the lower ranges.

DR. VAN METER: With LASIK.

DR. MC CULLEY: With anything.

Dr. Pulido?

DR. PULIDO: I would like the labeling to say that there were too few cases above 10 diopters of myopia and/or 3 diopters of astigmatism to determine the safety, to completely determine the safety and efficacy.

DR. BULLIMORE: Mr. Chairman, a point of clarification here. The question No. 2 that is on the screen which is the one I made a motion about refers specifically to stability. It actually is No. 3 on the Panel's handout. So, this may be leading to some confusion.

DR. MC CULLEY: Yes. The handout No. 2 is No. 3. No. 3 is No. 2. Sorry. So, the response to this question, Dr. Bullimore suggested the response and accepted Dr. Macsai's friendly amendment to that. Would you state that now?

DR. BULLIMORE: Basically that the sponsor has shown adequate stability with the conditions that stability

may be poorer above minus 7 diopters and stability has not been studied beyond 6 months.

DR. MC CULLEY: Okay, is there agreement? Okay, next question, No. 3, which is No. 2 on the written handout.

No. 3, do the clinical data in this PMA provide reasonable assurance of the safety and efficacy of LASIK for the correction of myopia with or without astigmatism in the ranges indicated.

Dr. Pulido?

DR. PULIDO: Now, I would propose a motion that the labeling say that there were too few cases above 10 diopters of myopia and/or 3 diopters of astigmatism to completely determine the safety and efficacy in this range.

DR. MC CULLEY: Does that meet with approval?

DR. VAN METER: That is just a fact, and then we don't approve safety and efficacy above minus 10. That is not a labeling issue.

DR. MC CULLEY: You stated it as a labeling and that is a good point, Woody, thank you. We want to set range, a recommendation for approvable and as I looked at things between 10 and 14 there were questions that you would address with the labeling as you have suggested, but there were no patients above 14 and there were no patients with astigmatism greater than 4 in the study. So, I don't see

that we can approve something where we have zero data. It seems like with no data above 14, no data above 4 in cylinder that we cannot assess that because we have zero data to try to assess.

Dr. Macsai?

DR. MACSAI: Jim, we have I think two patients. It wasn't zero patients over 4 diopters. It was just two patients over 4 diopters. So, it was --

DR. MC CULLEY: Let me ask the table. How many patients above 4 diopters of astigmatism?

PARTICIPANT: Two.

DR. MC CULLEY: Were there two between 4 and 5?

DR. ROSENTHAL: Mr. Chairman, excuse me. Dr. Waxler cogently reminded me there are indications in which you would name the range and then there is the labeling which would make certain statements about those outside the range.

PARTICIPANT: Here are the numbers you requested. There were 9 between 3 and 4 diopters and 2 between 4 and 5 diopters of cylinder.

PARTICIPANT: Nine between 5 and 6.

DR. MC CULLEY: Okay.

Dr. Bullimore?

DR. BULLIMORE: Do we have a motion before us at

the moment? If not, I would like to make one.

DR. MC CULLEY: We are not to formal voting, but if you would like to restate our consensus answer to the question that would be good.

DR. BULLIMORE: I will restate the consensus. I think the indications should say that the range should be up to minus 10 for sphere and the cylinder should be up to 4 diopters, minus 4, but I will accept friendly amendment.

DR. MC CULLEY: Is there agreement with that or should it be, but I am confused by what you said before that we can have indications but then we can have labeling that allows going beyond the indication. I thought we would have ranges and then there would be labeling warnings about areas within the range. So, let us go with ranges and warnings within the range because that is more like I think we have done it before.

DR. PULIDO: I second Dr. McCulley's motion to have ranges and labeling within the range.

DR. MC CULLEY: Dr. Macsai?

DR. MACSAI: I agree with you but since there are no patients over 5 diopters I would feel very uncomfortable with that range.

DR. MC CULLEY: That is fine. We are trying to get a principle set here. So, if you agree with the principle,

then we will try to set the ranges. Okay?

DR. ROSENTHAL: Excuse me, if I am not mistaken you have in fact set a range and then made a recommendation above the upper level of the range.

DR. MC CULLEY: Let us do it this way.

DR. ROSENTHAL: You can do it either way you want and we are happy to take your recommendation.

DR. MC CULLEY: Let us do it this way today and then you can deal with it however you want to. What do we want the range to be, up to what in sphere? I heard Dr. Mannis before say, "Up to 14 with label warnings" or label warnings above 10 anyway. Maybe you didn't say, "Fourteen." They had data to 14.

DR. MANNIS: I didn't say, "Fourteen."

DR. MC CULLEY: Okay, he said, "Above 10 warnings." So, I got the 14 from another piece of it.

DR. MANNIS: Actually mine was lower. It was above 7.

DR. FERRIS: I would recommend up to minus 12.

DR. MC CULLEY: Minus 12 on the sphere.

DR. BULLIMORE: Mr. Chairman as the secretary is it my responsibility to take a weighted mean for this?

DR. MC CULLEY: You are going to lose more hair.

PARTICIPANT: Is that spherical equivalent or

sphere? I didn't hear what you said.

DR. BULLIMORE: Sphere.

DR. MC CULLEY: Okay, Dr. Wang?

DR. WANG: I would say just minus 12 and minus 4 cylinder.

DR. MC CULLEY: Woody?

DR. VAN METER: That than allows a minus 16 plus 4 which I think is outside the intent of what we mean. So, a patient who is minus 16 plus 4 would be correct by letter of the law but not by the intent.

DR. MC CULLEY: That is not necessarily true with the manner in which this laser treats myopia. You will not be removing a minus 16, 17 amount of tissue.

DR. VAN METER: I understand, but I mean should we add a spherical equivalent?

DR. MC CULLEY: We were talking about sphere minus 12 and cylinder 4. Is there general agreement with that?

DR. ROSENTHAL: And again Dr. Waxler reminds me that is what the laser that you are currently considering is labeled for PRK.

DR. MC CULLEY: Isn't it amazing how consistent we are?

DR. ROSENTHAL: Isn't it amazing.

DR. MC CULLEY: Up to minus 12 and a minus 4

cylinder; is there agreement with that, and that is nice to hear that it is consistent with the current labeling.

Dr. Macsai?

DR. MACSAI: Maybe the sponsor cannot tell me because I think it is out of order, but maybe the Panel members, someone could answer the question for me, what are the microns of tissue removed at a minus 12, minus 4 correction?

DR. MC CULLEY: At a 6, I can tell you what I have in my memory bank that you are removing roughly 11 microns per diopter at a 6-millimeter zone. The zone is going to be less in treating the cylinder.

DR. ODRITCH(?): I am Mark Odritch. I am the sponsor --

DR. MC CULLEY: You are out of order, Mark.

DR. WANG: So, focal equivalent in that case is minus 14 and 12 microns per diopter. So, 12 times 14 is total microns tissue removed.

DR. MC CULLEY: But we are going to come to the critical issue here. We are going to come to the critical here on the untouched posterior stroma. That is the issue, and we are going to get that issue, that concern dealt with otherwise. So, I don't think that the exact answer to that question is relevant. So, we will deal with it otherwise. I

am not going to recognize anyone from the audience.

DR. SUGAR: Assuming that we just agreed to that, the minus 12, minus 4, can we as a corollary to that request that the labeling have specific tables showing outcomes for the different ranges?

DR. MC CULLEY: We have done that before that in the labeling that there be stratified and I think that is a suggestion that we have agreed was good in the past, and I think it is good in this setting as well.

Dr. Macsai?

DR. MACSAI: Dr. McCulley, could I add that that be stratified by 1 or 2 diopters, not by less than 7 and greater than 7?

DR. MC CULLEY: Yes. Does the Panel agree with that? That is what we have done. That is consistent with prior. So, it would be stratified by 1 or 2, Marian. You have to pick.

DR. MACSAI: One.

DR. MC CULLEY: By 1 diopter. That is recommendation. If reality proves that that is not practical, the FDA can deal with that. We are making recommendations for FDA.

DR. PULIDO: Dr. McCulley, does the Panel feel that adding further verbiage besides just a table saying

that cases above 10 diopters, there are too few cases above 10 diopters and 3 diopters of astigmatism to completely determine the safety and efficacy in these ranges?

DR. MC CULLEY: I think that is reasonable. Others, I think Mark had that actually in his written review.

Is there concurrence with that?

Okay.

DR. MACSAI: May I ask a question regarding the range? Within the range are we going to specify the 250 microns of tissue or --

DR. MC CULLEY: Marian, that is his question.

DR. MACSAI: Okay.

DR. LEPRI: Question 4, what are the Panel's recommendations regarding the data on the individualized nomogram used in this investigation of LASIK?

DR. MC CULLEY: Can you read for us exactly what the sponsor is requesting the labeling to be relative to the nomogram?

DR. LEPRI: The programmed amount indicates the average correction that can be anticipated but actual use may require individual adjustments at this amount. Tracking of clinical outcomes is recommended.

DR. MC CULLEY: I have a question for you on that.

That implies that the software in the laser is going to be changed for LASIK as opposed to a PRK setting.

DR. LEPRI: My understanding is that the software isn't changed but the amount -- they have specific settings in software for LASIK. However they are going to change the amount of intended correction that is cranked in based on an analysis of the beginning patients.

DR. MC CULLEY: Of the nomogram?

DR. LEPRI: Of the nomogram.

DR. MC CULLEY: So, what they are saying is that there will be -- that doesn't address the nomogram. How does one get to the programmed amount? That is the nomogram that gets you to the programmed amount and then based on individual experience one may have to adjust that. What is said about getting to the programmed amount?

DR. LEPRI: There is a look-up table included in the PMA that shows in 1 diopter stratifications the results of this clinical investigation for each area of spherocylindrical correction, what should be cranked in and what the standard deviations were. So, they had to write in mean values.

DR. MC CULLEY: And that will be part of the product labeling?

DR. LEPRI: Yes. That is my question. Should it

be part of the product labeling?

DR. MC CULLEY: Absolutely.

DR. BULLIMORE: I think we are in agreement there.

DR. MC CULLEY: And that you may have to make individual adjustments from that. Okay.

Yes, if what I understand you to be saying is what you are saying that sounds appropriate.

Is there agreement with that?

DR. FERRIS: Was it may require individual adjustments or did require individual adjustments.

DR. MC CULLEY: May require.

DR. LEPRI: It will depend on the -- it is an outcome-based nomogram program adjustment. There were varying amounts of adjustment and someone may out there in the world, but my understanding is, not need to make an adjustment.

DR. MC CULLEY: I guess what Rick is saying was there indeed a person who did not have to make adjustments. So, should it be may or will?

(There was a chorus of "May.")

DR. MC CULLEY: All right. Dr. Wang?

DR. WANG: I have a suggestion for amendment to this based on I overall agree with the way this is approached. You can take advantage of the large generic

nomogram based on 1000 patients, yet, also, take into account the patient-specific techniques and whatever. However, there is an intrinsic assumption in this approach, that is assuming the surgeon's ratio to the generic population remains constant, in other words personal calibration factor always stays at .9 for Joe Smith, the surgeon. So, therefore, I don't know whether the surgeons may not really understand that. It has to be very important that the surgeon has to keep the same surgical technique, room humidity, temperature, various conditions so that within the surgeon that he or she will be operating with the same personal calibration normalizing factors. So, maybe a language or two stressing the need that the surgeon has to maintain intrasurgeon consistency in order to use this ratio consistently.

DR. MC CULLEY: If we are going to take it to that degree one would have to say that the surgeon has to be aware that this is surgeon technique, that that individual surgeon's technique has laser dependency, has the laser exactly as at the time and the environment must not change. So, I think we can leave that to the FDA as to whether those additional factors would need to go in there. That is a good point.

DR. LEPRI: It could be added to have continued

tracking of clinical outcomes it is recommended, so that some --

DR. MC CULLEY: Or you can state what the variables are. Dr. Wang is correct, that the nomogram can change, if the same surgeon everything being the same changes his technique somewhat.

Mark?

DR. MANNIS: Mark Mannis. Is recommended in this statement a strong enough word? Should we perhaps say, "Necessary" or "Mandatory" because the only way you can modify your nomogram is to track your clinical outcomes? So, it really is saying that in order to do this accurately we shouldn't just recommend that they track clinical outcomes. If you want to have an accurate system of delivery you have got to monitor your outcomes.

DR. MC CULLEY: This gets into management issues for the FDA. I think, can we leave that as you guys think about that rather than us coming down on it? That has implications I think beyond --

DR. FERRIS: Rick Ferris. I just want to go back to the word "may" because I know you cannot write a sentence that everybody understands, and this one I don't understand in a way that may be different than other people don't understand it and that is I view in this PMA that they

presented it did require individual adjustments and they showed us data that showed that each individual had to adjust their machine. Now, that adjustment may be close to zero or zero, but they had to look at it and adjust it, and the way to me means, well, maybe you don't have to do that.

DR. MC CULLEY: May I suggest, "Will probably" or something of, I think will probably require. I don't know if that is -- you understand our concern about this, and I think we all agree with Dr. Ferris. You have words that I am sure you are more allowed to use or otherwise. Get the point? Okay.

DR. LEPRI: Stronger language.

DR. MC CULLEY: Stronger language.

Next question?

DR. LEPRI: No. 5, does the Panel recommend including warnings in the labeling regarding post-LASIK corneal ectasia?

Dr. Sugar, would you like to suggest the wording for that?

DR. SUGAR: I suggest that the labeling contain a statement in that regard.

DR. MC CULLEY: Okay, Dr. Mannis had in his review, I believe it was Mark's, a --

PARTICIPANT: In Dr. Lepri's Page 11.

DR. MC CULLEY: Okay, iatrogenic corneal ectasia is a possible complication of LASIK. Clinical data suggest that this complication is uncommon with residual and I inserted there untouched or posterior corneal stroma, stromal thickness of at least 250 microns. Residual stromal thickness could be to the uninitiated, one could take into account the thickness of the flap. It is the posterior portion that is untouched. So, it needs to be wording that makes that clear that cannot be misinterpreted. So, it is not total. It is posterior untouched.

Dr. Wang?

DR. WANG: Ming Wang. I have a suggested amendment to that statement. I feel it is probably not strong enough, maybe something to the FDA recommends against performing this procedure, something to that effect while the residual point is the posterior stroma is less than 250, rather than state it is uncommon.

DR. MC CULLEY: I don't have a problem with that.

DR. MACSAI: I agree with that because if you are treating a minus 14 spherical equivalent to have a 250-micron bed you need a corneal thickness of 580.

DR. MC CULLEY: Right.

DR. MACSAI: Five hundred and eighty microns and you may not have that in some individuals.

DR. MC CULLEY: That is right. That is why we have, and that was, I think that needs to be strongly stated that the posterior 250 microns not be invaded because of the fear of second corneal ectasia, and one has to be very careful and the safest way to do it is run the thing on the laser to see how many microns it says it is going to take off and create a table, and you have the table there with you, and you can look and see and look at how much corneal thickness there is, that is pre-op to know whether you can do it, but that is the safest way to do it rather than doing it with calculations and formula.

Okay, so we have answers to all of your questions. Do you have any other questions, and Dr. Rosenthal, no confusing questions.

Okay, Dr. Sugar?

DR. SUGAR: Can we have additions?

DR. MC CULLEY: Yes.

DR. SUGAR: I would like to add that there be a statement concerning the possible adverse effect of pupil size on patient's symptoms and that this be taken into account and this be placed both in the patient brochure and the physician labeling.

DR. MC CULLEY: Okay, and Dr. Bullimore you had, we had a couple that you were scribing. Dr. Matoba had one,

and then we had one other that brought product labeling in line. You didn't write it, huh? Okay, he will write it this time, Alice.

DR. MATOBA: My suggestion was that the labeling be modified to be consistent with the exclusion criteria that were used for the clinical trial, specifically previous intraocular procedures, surgery. Patients with that indication were excluded.

DR. MC CULLEY: Why?

DR. MATOBA: I don't know why, but I think that there should be a warning. It shouldn't necessarily be an exclusion criterion in the labeling, but it should be a caution that this procedure was not investigated for those subgroups.

DR. MC CULLEY: And the why is you can blow the wound, but anyway let us not. I should just shut up.

Dr. Wang?

DR. WANG: I would like to suggest in the same paragraph Dr. Sugar suggested adding a sentence saying that cautionary statements such as for high range of correction visually significant halo or glaring may be present.

DR. MACSAI: Dr. McCulley?

DR. MC CULLEY: Is there agreement with that?

DR. MACSAI; I would like to expand on it.

DR. MC CULLEY: I will recognize you in a moment, Dr. Macsai.

Is there agreement with that?

Okay, Dr. Macsai?

DR. MACSAI: I think we need to expand upon that and actually include the percentages that were shown in the study of glare and halos that patients experienced.

DR. MC CULLEY: Is there agreement with that?

Okay. Any other additions?

I will ask the consumer rep, do you have any other additional comments you would like to make?

MS. MORRIS: Lynn Morris. I wanted to be clear that pupil size was included. I thought I heard the sponsor say that that wasn't part of the study. They didn't collect that data.

DR. MC CULLEY: That is correct. They did not study it, but the fact that they did not study it does not alleviate our concern that it might be an issue. So, we are saying that we want that in.

MS. MORRIS: Oh, no, I want you to assure me that that is going to be in the labeling.

DR. MC CULLEY: Yes, that was added.

Are there any other additions?

Before a motion is entertained the Chair will open

the floor for open public comment. The period will not exceed more than 30 minutes and individual speakers will be limited to a maximum of 5 minutes.

Is there anyone from the public that would like to come back and make a comment? Are you public or are you sponsor?

PARTICIPANT: I am public, really.

DR. MC CULLEY: I know who he is. Yes, you may return to the podium.

DR. STONECIPHER: Just real quick, my name is Dr. Karl Stonecipher, and I just want to clarify a couple of things. I think you guys have answered that the higher myops, they tend to be more happy, and those patients tend to have less out- -- better outcomes. So, I think you stated that, and I think that is good. One thing that I think has been brought up with everybody, you have got to remember this is a mobile population. I mean it is a very mobile and this was written as a 6-month study, and correct me if I am wrong but that was the way that the informed consent was read, and the higher myops tend to sometimes have this anatomic disparity, and we included that, whether they had 20/40 vision or whether they had 20/30 vision, but they were still based on that original 20/20 guideline and then one thing that is very important and I think that we

missing and we haven't seen it in the discussion of the Panel, Mr. Link's comments earlier are very important. I agree that glare and halos are very important. We need to look at pupil size although we didn't do that and maybe you want to do that in your labeling, but the most important problem that is brought up here is that we have some ethical guidelines that we need to look at and be a patient's advocate that need to be addressed, that like Dr. Ferris brought up aren't going to be addressed. I mean whether you guys approve it or not, they are still going to keep doing it, and if you put some kind of guidelines out there then whatever governmental agencies will be able to put those guidelines into place.

Thank you.

DR. MC CULLEY: Anyone else who would like to make a comment from the audience?

Seeing none, the -- I didn't see your hand, sorry.

Identify yourself?

MR. LINK: Ron Link. I just wanted to say that it was very good to be here today, and I am coming away with a much better feeling to go back to my rank and file, if you will of the willingness to listen to our concerns and address them and I think one thing that is clear to me is that LASIK is a procedure obviously that is here to stay and

I have friends who have had success with it. I am very happy for them. At the same time the people who have poor outcomes, there needs to be more research as to what to do with these people in terms of fixing them, you know in just really blunt terms because their experiences, they go back to the doctor and they are met with well you should maybe wait until the technology improves or we will send you up to Canada or any number of suggestions.

So, a lot of them are in holding patterns and some for years, and I think given the overwhelming success of the industry and the money that has been generated it would be an ethical imperative to donate some of that profit to research to help those who didn't have the good outcome.

DR. MC CULLEY: Thank you for your comments. You realize we have no control over that?

MR. LINK: Absolutely. I just wanted to make it a matter of public record.

Thank you.

DR. MC CULLEY: Any other comments from the public?

Seeing none, the open public hearing is now closed.

Does the FDA have any closing comments?

(No response.)

DR. MC CULLEY: This is new. Does the sponsor have any closing comments?

You have 5 minutes.

DR. ELDRIDGE: Sorry for that interruption, Mark Eldridge. I represent VISX. I am the medical monitor to VISX and a paid consultant to VISX. Several concerns were brought up by the Panel. We are here with, we being VISX, not me. VISX is here with this sponsor, and we would like to point out a couple of things. The concern regarding the minus 16, plus 4, I would like to answer numerically so the Panel is comfortable with it. A minus 14, minus 4 ablates 140 microns of tissue. Monolin's(?) formula is based on a 12-micron per diopter ablation at 6 millimeters. Ours is a multizone ablation. So, it has less than the numeric guide that you see if you just did the math.

Secondly, our technology uses a set of slits that affords us to create a shape that does not ablate any deeper whether you are doing a minus 12 sphere or a minus 12, minus 4. So, when you program in minus 12 sphere it is 140 microns. When you program in minus 12, minus 4, it is 140 microns. Interestingly when you go to 6 there is a little bit more of an adjustment which has to do with a nomogram factor internal in the laser. It only goes to 147. So, if you program in minus 12, minus 6 it will be 147 microns of

tissue that are ablated. Minus 12 which is, the issue that we are talking about is 127 microns of tissue. So, minus 14 is 140. Minus 12 is 127 and adding sphere up to 4 does not increase the ablation depth. I am sorry, cylinder, up to 4 does not increase the ablation depth which is the reason the spherical equivalent does not make sense in this particular device. It becomes cumbersome and very difficult for the clinician to figure out. It is not quite straightforward. So, I applaud you if you should elect to go with a minus 12 sphere or minus 14 sphere and whatever cylinder, but understand that that is a minute increase. That is issue one.

Issue No. 2 has to do with asking the sponsor, in this case CRS to go back. I can tell you having been the monitor for VISX when we had to go back for PRK and several other times that every time we have gone back we have had significant problems and the problems have to do with the fact that the investigators are the ones who have a moral, ethical and medical-legal responsibility to the patients. We do not, okay? And as a company, a sponsor, it is very hard to go back directly to a patient, and I think CRS is to be applauded for having attempted to motivate their surgeons. Additionally every time we have done it, it has only shown and verified exactly what CRS has showed you, that those

patients are doing better. It is when they don't do well they show up at your doorstep.

Guy?

DR. KEZIRIAN: In my 1 remaining minute I just wanted to thank the Panel for your discussion and your consideration of the application. We have worked very hard to try to present it in a way which was understandable, and I think you perceived that our approach has been to lay forward our work on the table for you to observe, and we did not start this with the understanding or intention of being able to affect a labeling change. If we can, we have succeeded more than we wanted to. Our attempt was to validate LASIK, and we feel we have.

Now, with the issue about the patients that we couldn't show you through 6 months, I hope that you have had the opportunity to look at Table 8 which is this last visit carried forward analysis. It basically takes the last time we saw them and says how they were doing.

Seeing that patients haven't changed in any other part of this cohort, we did see them postoperatively, almost all of them were seen postoperatively, I would say that all of them were seen postoperatively and reported. So, they are all in there, and the results didn't vary very much. So, I just wanted to point that out that the information is there

as much as we could possibly generate it and again, thank you for your consideration of this work.

DR. MC CULLEY: Thank you.

Ms. Thornton will now read the voting options for us.

MS. THORNTON; The Medical Device Amendments of the Federal Food, Drug and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an outside expert advisory panel on designated medical device premarket approval applications or PMAs that are filed with the agency.

The PMA must stand on its own merits, and the Panel's recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions of intended use outweigh any probable risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population the use of the device for its intended use and conditions of use when labeled will provide clinically significant results.

The Panel's recommendation options for the vote are as follows: No. 1, approval. There are no conditions attached.

No. 2, approvable with conditions. The Panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes or further analysis of existing data.

Prior to voting all the conditions are discussed by the Panel and listed by the Panel Chair.

No. 3, not approvable. The Panel may recommend that the PMA is not approvable if the data do not provide reasonable assurance that the device is safe or if a reasonable assurance has not been given that the device is effective, under the conditions of use prescribed, recommended or suggested in the proposed labeling.

Thank you, Dr. McCulley.

DR. MC CULLEY: Dr. Bullimore, would you like to make a motion?

DR. BULLIMORE: I will try. This is Dr. Bullimore.

I move that the PMA be deemed approvable with the following conditions, that the range be limited to minus 12 diopters sphere and 4 diopters cylinder and that the labeling include the following: No. 1, safety and efficacy

data be presented, stratified in 1-diopter steps and a clear statement included to indicate that poorer outcomes should be anticipated in refractive errors above minus 10 diopters.

Two, that stability though established is poorer in corrections above minus 7 diopters and has not been studied or established beyond 6 months.

Three, there is a need for a nomogram to determine the correction as worded by the sponsor on the slide.

Four, that the residual posterior corneal stroma of a depth of 250 microns not be invaded by either the laser and/or the microkeratome.

Five, caution be exercised in patients with prior intraocular surgery.

Six, some patients will experience significant visual symptoms such as glare and halos. These may be worse in patients with larger pupils or in conditions where the pupil is dilated.

Have I missed anything?

DR. MC CULLEY: That is your motion?

Is there a second to the motion?

DR. HIGGINBOTHAM: Second.

DR. MC CULLEY: Is there further discussion on the motion?

DR. HIGGINBOTHAM: Just a minor refinement and a

friendly amendment. Incisional intraocular surgery, just to not include within that cautionary statement laser surgery.

DR. BULLIMORE: I accept that friendly amendment.

DR. MC CULLEY: Dr. Macsai, I thought I saw your hand or was it Woody?

I saw a hand down there.

DR. VAN METER: It was the question of accountability was not mentioned among the provisions, is that correct?

DR. MC CULLEY: The motion on the table did not have --

DR. VAN METER: Was there not a straw vote that --

DR. BULLIMORE: I will entertain friendly amendments on the topic.

DR. MC CULLEY: We never reached consensus.

DR. VAN METER: Is the agency happy with where we stand on accountability?

DR. ROSENTHAL: I don't know that that is an appropriate question.

DR. MC CULLEY: I think we have a motion on the floor. It has been seconded. It is under discussion.

Dr. Pulido?

DR. PULIDO: I would like to add an amendment to it, and that is contingent upon some say 20 percent data

from the remainder cohort that can be obtained by phone showing similar patient satisfaction to those in the PMA cohort.

DR. MC CULLEY: Do you accept that friendly amendment?

DR. BULLIMORE: I don't accept the friendly amendment and here is why. Basically what we are criticizing the sponsor for and our criticisms may be justified or not is less than adequate science in their accountability of their subjects. I am worried that in setting any conditions that we really be guilty of the same thing, and we would be setting arbitrary targets, drawing lines in the sand that really we don't have a sound basis, and they might be seen as just nothing more than hoops that we want the sponsor to jump through. So, with due respect, Dr. Pulido, I don't accept your amendment.

DR. MC CULLEY: If I am correct, what we do now is the Panel needs to vote as to whether it wishes to include that amendment in the motion, not whether you are voting on the motion but voting on the amendment.

All those in favor of the amendment raise your hand?

PARTICIPANT: What is the amendment?

DR. MC CULLEY: The amendment to have a 20 percent

assessment of those lost to follow-up. Dr. Bullimore has not accepted it as a friendly amendment.

Does the Panel feel that, you need to vote yea or nay as to whether that amendment should be added as I understand the proceedings.

All those in favor of that amendment raise your hand?

(There was a hand.)

DR. MC CULLEY: You are consistent.

All those opposed?

(There was a show of hands.)

DR. MC CULLEY: The amendment is defeated.

Further discussion on the motion on the floor?

DR. VAN METER: I would like to make an amendment that we ask for 90 percent accountability at 6 months.

DR. MC CULLEY: Is there further discussion on -- do you accept that as a friendly amendment?

DR. BULLIMORE: With due respect to Dr. Van Meter, I decline to accept that.

DR. MC CULLEY: Is there further discussion on the proposed amendment?

Those in favor of the amendment raise your hand?

(There were six hands.)

DR. MC CULLEY: Those opposed?

(There were four hands.)

PARTICIPANT: Can you do it again?

DR. MC CULLEY: Let us do it again.

Raise your hand high, those in favor of -- restate the amendment.

DR. VAN METER: I would like to ask for 90 percent accountability of patients at 6 months.

DR. WANG: A point of clarification, is that 90 percent accountability of the PMA cohort or of all eyes?

DR. VAN METER: We have 76.3 percent accountability of the PMA cohort at 6 months, and I would like 90 percent accountability of the PMA cohort.

DR. WANG: So, that would not include the remainder cohort?

DR. VAN METER: That would not include the remainder cohort.

DR. MC CULLEY: Further discussion on the amendment?

Okay, Dr. Wang?

DR. WANG: That would entail additional study because obviously with the current data set that is not there.

DR. MC CULLEY: Further discussion?

Those in favor of the amendment -- you had further

discussion?

DR. BULLIMORE: I just think this is an unreasonable, unrealistic target for the sponsor to fulfill. So, I will continue to vote against the amendment.

DR. VAN METER: I would like some discussion on why it is unreasonable and could you tell me why we are changing, why you are happy with less than 90 percent data now when you have not been happy in the past?

DR. BULLIMORE: You put me on the spot, Woody. As identified by the Chair at the beginning of this proceedings we are dealing with a procedure here which has probably been performed on 100, 200, maybe 300 or more thousand Americans and then performed by many people sitting around this table. So, it is with that that I am sort of coloring my perspective on this PMA.

I think my previous comments notwithstanding the fault I don't believe is with the sponsor per se. There are one, actually two investigators that really did them in.

DR. VAN METER: I agree.

DR. BULLIMORE: Who are responsible for 25 percent of the total cohort. If you look beyond that to the PMA cohort you see pretty good accountability at 3 months across the board. I would like to see it higher at 6 months, but we may be presenting something to the agency that they either

have to go against or that the sponsor may not be able to meet.

DR. MC CULLEY: Woody, I can tell you what gives me some degree of comfort. There was 90 percent accountability at 3 months and stability was reached at 3 months. My judgment of that gives me sufficient degree of comfort, but I will only be voting to break a tie.

DR. VAN METER: I understand. The issue becomes that we don't have any information on a certain subset of patients, and I would like to get some information on those patients. Now, I realize the 6-month data is not obtainable, but I think it is possible for some communication with these patients to be attainable or some examination.

Now, the reason I voted against Jose's amendment was I think 20 percent telephone is inadequate, but if you can make contact with 90 percent of the patients then perhaps that would be adequate.

DR. MC CULLEY: So, clarify your request. It is not necessarily full data at 6 months. It is some accountability with those --

DR. VAN METER: I would like to have 90 percent accountability, accountability of 90 percent of the patients after 6 months. Now, 6-month data is not possible now, and

within what is possible can we get some information on these patients that we don't have information on?

DR. BULLIMORE: Mr. Chairman, maybe a little clarification as to Dr. Van Meter's intent; is this to assure the safety and efficacy of this particular PMA or is this colored by the desire to have more complete data in future PMAs?

DR. VAN METER: Both. My comments are colored by the fact that I am concerned about patients that don't do well, and we had testimony this morning about a few patients, a very few patients that have problems with this procedure afterwards. One way to keep this from happening is to have very adequate informed consent that people know what they are getting into.

It appalls me that a heart medication which is necessary to preserve life may have a few paragraphs of what is good about it and then two pages of what is bad about it. Here is something that affects the visual system, and somebody has to live with it. We are not talking about a life-threatening disease.

In order to make patients aware of an informed consent I think we need to have better data than we have and my concern is that some patients are slipping through the cracks. It is a wonderful procedure. It is widely

advertised. I know people are going to do it no matter what we say, but I would like to have some information on this particular set of patients that all is well.

DR. MC CULLEY: Dr. Rosenthal?

DR. ROSENTHAL: I don't think anybody wants that more than the agency as well. I think the issue is that the agency regulates the companies and the companies must provide a balanced view of the issues. We do not regulate doctors in their offices and we do not regulate what doctors advertise. We regulate companies and the company's responsibility is to put in their labeling all the issues related to all the things you were talking about, and that accompanies, in this instance there is a laser, and I don't know what is going to happen with the PMA, but there is a laser and if that company ultimately adopt that PMA they will have to put in the information that was obtained from the data that was generated.

If you think that in fact that data is biased then you must request additional information. If in fact, you want it for, I don't know, consistency's sake, then you must request that information.

I think the issue is one of, and Rick said it more eloquently than I did, one of public health. There is a procedure being done 400,000 times a year in this country

and there is no information, and I am not making one side or the other. It is your decision to make, and I respect your decision, but I would like you to weigh a device that is new to the system in which there is no information in which there is no question the highest standards must be obtained and a device or an indication for a device which is being used widely throughout this country in which there are no indications for use, no information that is being publicly provided for by either a government agency or by an organization or something like that. I just ask you to take that into consideration.

DR. VAN METER: I understand what you are saying, and Mr. Chairman, I accept the accountability data.

DR. MC CULLEY: You withdraw your --

DR. VAN METER: I withdraw.

DR. MC CULLEY: Your friendly amendment?

DR. VAN METER: I withdraw my friendly amendment.

DR. MC CULLEY: That, I believe is allowable by Robert's rules of order.

So, that friendly amendment is withdrawn.

Dr. Pulido?

DR. PULIDO: I would like to propose a separate amendment and that would be that labeling would say, "Accountability data after 6 months is insufficient to

determine long-term safety and efficacy.

DR. MC CULLEY: We had something about 6 months before. Does what we had before, royal scribe, cover it? We need more?

DR. BULLIMORE: I accept that friendly amendment.

DR. MC CULLEY: Okay, is there further discussion on this amendment, and then I will get to Marian.

Dr. Wang?

DR. WANG: Ming Wang. I just want to second Dr. Bullimore's. I think even though there is a technical difference between 80 and 90 percent, but this procedure has turned out to be by and large a reasonable, efficacious and safe procedure. I understand Dr. Ferris' concern about possibility of unknown bad complications lurking out there, but I think the possibility with LASIK based on clinical experience is probably small for this particular PMA.

I don't think we need to worry about setting a precedent in terms of 80 percent. Each PMA is different as Dr. McCulley pointed out. So, I will support no additional data is needed.

DR. MC CULLEY: Further discussion on the amendment?

DR. BULLIMORE: Could I read it back as I have it before we put it to bed? The seventh labeling condition be

a statement that approval and data was based on 76 percent accountability at 6 months or beyond.

DR. MC CULLEY: Are there any further amendments, discussion?

MS. MORRIS: I am sorry to complicate this. I need to ask, Lynn Morris. I need to ask a procedural question here. I have had some of the same concerns that were mentioned earlier about informed consent and I have held up talking about it because I wasn't sure whether it should be a labeling issue. So, before you vote and close this issue off I want some sort of direction from you on whether that issue will be discussed in some other way or whether that needs to be discussed in the labeling issue.

DR. MC CULLEY: Good point, and I am not sure how to answer.

Dr. Rosenthal?

DR. ROSENTHAL: I think I can answer. We do not regulate the practice of medicine.

MS. MORRIS: Oh, I understand that.

DR. ROSENTHAL: We do not tell a doctor what he can put in his informed consent, but if we have in a labeling that there are certain concerns and there are certain issues, then it is up to the doctor to make the decision how he wants to present it to his patient and how

he doesn't want to present it to his patient. That is all we can do.

MS. MORRIS: But is it our responsibility to recommend in practitioner labeling or instructions something that we would want in the informed consent?

DR. ROSENTHAL: Dr. Waxler just told me there will be a patient labeling brochure in which information that the company will be required to --

MS. MORRIS: I understand that.

DR. ROSENTHAL: -- make sure the patient gets it. Whether the doctor gives it to the patient or not --

MS. MORRIS: What I am asking is not in the patient information book but in the practitioner information.

DR. MC CULLEY: You mean the information provided to the physician?

MS. MORRIS: That is right. So, can we make, I mean is this the point in the discussion where we should be making recommendations on how we want a physician to use the informed consent document?

DR. MC CULLEY: My impression is that I think that is wonderful, but I don't think that it is --

MS. MORRIS: That is what I am asking you, procedurally can we do that or not?

DR. ROSENTHAL: I am afraid it is not the purview of the agency.

MS. MORRIS: We cannot recommend things in practitioner information?

DR. ROSENTHAL: We cannot tell them how to write an informed consent. We can tell them what the labeling issues are with respect to the device, the adverse events, the complications, the potential hazards, and we can embolden it in big bright blue letters, but if a doctor does not want to tell it to the patient, we cannot tell him to do so.

DR. MC CULLEY: The check and balance in the system for that physician who does not is our legal system.

DR. ROSENTHAL: I am afraid.

DR. MC CULLEY: Other discussion?

All right, we have a motion on the floor for approvable with the conditions that have been read into the record, and it has been seconded.

DR. VAN METER: We have not voted on Dr. Pulido's amendment.

DR. BULLIMORE: I accepted it as a friendly amendment.

All of those in favor of the motion, please raise your hand high?

(There was a show of hands.)

DR. MC CULLEY: Nine.

All those opposed, please raise your hand high?

(No response.)

DR. MC CULLEY: Two abstentions. There were none and so obviously by simple math, two abstentions.

Now, each person will be asked to indicate why you voted as you voted or I guess abstained as you abstained.

We will start with Dr. Wang.

Identify yourself each time.

DR. WANG: This is Ming Wang. I voted to approve with conditions as outlined by Dr. Bullimore as I feel the sponsor has done an adequate study in addressing some major concerns regarding safety and efficacy of this procedure.

DR. MANNIS: Mark Mannis, likewise I vote in favor of the recommendation based on the data provided us in the study which I felt was adequate for safety and efficacy.

DR. MATOBA: Alice Matoba. I voted in favor of the motion and I, also, feel that the study did show adequate safety and efficacy.

DR. BULLIMORE: Mark Bullimore. I voted yes. I do have a number of residual concerns, most of which are covered within the labeling.

DR. SUGAR: I voted yes, as well. This is a real-

world study and it was done, I think in a relatively unique way with multiple surgeons funding their own investigation. This provides us with an opportunity to set standards and set the position of the bar for the future for this technique, and I am in favor of it.

DR. PULIDO: I voted yes only after I was able to get some amendment showing that accountability was poor because that was a real problem with the study, and again I don't want to see this kind of study brought forward in the future.

DR. HIGGINBOTHAM: I voted yes because the stated conditions do cover my concerns including the accountability issue which has been covered, and I applaud the physicians for their initiative in bringing this to the Panel.

DR. JURKUS: Jan Jurkus. I voted yes because I believe this information is very much needed regarding LASIK surgery for both the practitioners and the public.

DR. MACSAI: Marian Macsai. I abstained because there is a body of information out there that is in the scientific literature that has undergone peer review regarding this subject which provides knowledge regarding the procedure. However, I cannot recommend approval of this PMA because I cannot assess that true safety and efficacy has been established due to the lack of accountability.

DR. VAN METER: Woodford Van Meter. I voted approvable with conditions. I am concerned about the accountability issue, but I realize that taking the sponsors at their word this information likely is not obtainable, and I don't wish to visit the sins of a few investigators on the sponsor. I am, also, concerned about informed consent as patients view this with the barrage of advertising that even though it is not under the purview of this agency or this committee is outside the range of this discussion, but it concerns me, nonetheless. I hope we don't have a whole lot more patients with accounts like we heard this morning come forward with LASIK.

DR. FERRIS: Rick Ferris. I abstained from the vote because it is my belief that the data that were included in this PMA are not scientifically adequate for approval. However, I note that while we have been yammering about this probably hundreds of these procedures have been done this morning, and that there are other people on this Panel with personal experience and, also, knowledge from other individuals and reports that I don't have as a poor retina person that make me not want to vote against it because I don't have that information, and I acknowledge that their knowledge is better than mine in this area.

DR. MC CULLEY: Thank you.

Ms. Thornton has a couple of messages.

MS. THORNTON: Three to be exact. This is for the Panel. Will you please place the documents that pertain to this discussion this morning on PMA 990010 behind the Panel table, please, for collection.

I would like to remind those in the audience to please sign in. Also, I wanted to note there is a section in the restaurant reserved for FDA, about 25 seats to the far right of the restaurant.

Have a good lunch.

DR. MC CULLEY: Remember my admonition prior to the break and we will, by my watch, check yours relative to what it is, I have one-twenty-eight. We will start at two-twenty-five.

(Thereupon, at 1:28 p.m., a recess was taken until 2:25 p.m., the same day.)

A F T E R N O O N S E S S I O N (2:35 p.m.)

DR. MC CULLEY: I'll call the panel to order again. We will begin discussion on PMA P980051. I would like to welcome to the deliberations Dr. Mike Grimmett, and I'll ask Mike to introduce himself.

DR. GRIMMETT: Dr. Michael Grimmett from Bascom Palmer Eye Institute in Miami, Floor.

DR. MC CULLEY: I'd like to turn the floor now to the sponsor, who has 60 minutes to present your data.

Agenda Item: Sponsor Presentation of PMA P980051

DR. KOCH: Thank you, Dr. McCulley, and good afternoon everyone. My name is Doug Koch. It's a pleasure to be here with you to present the initial portion of this PMA from Sunrise Technologies. I am a paid consultant for Sunrise Technologies, but I am not a shareholder of the company. The other presenter this afternoon will be Doyle Stulting, and Dr. Till Anschuetz from Baden-Baden will be here to answer questions as well.

Before I begin, I would like to make two additional points regarding this PMA submission. The first one is that although I don't have a financial interest, I have a long vested interest in this topic. I began work on this 11 years ago personally. I started this work as a strong skeptic, not really believing that this technology or

any form of thermal keratoplasty could work. With time, as we improved the technology and began to gather data, I became a cautious optimist. I now stand before you as an enthusiast for what I think is an important technology.

Another point I would like to make is that all the data for this study were compiled and analyzed independently by an independent statistical firm.

And the third point that I'd like to make is that we are going to show you this afternoon data that I believe convincingly demonstrate the safety, efficacy, predictability, and believe it or not for thermal keratoplasty, stability that is acceptable, and certainly would justify the approval of this PMA.

The goal of this technology is to develop a procedure to correct hyperopia that is safe, effective, minimally invasive, provides high quality vision, and does not preclude other surgical procedures. The technology of thermal keratoplasty is now 101 years old, and multiple approaches have been tried in the twentieth century, as many of us already know. But basically all these non-laser approaches were abandoned for one primary problem, and that was that they were overheating corneas, resulting in scarring, epithelial problems, regression, irregular astigmatism, and other sorts of similar problems.

Lasers that have been studied include the CO₂ laser, hydrogen fluoride holmium, and continuous wave diode lasers. The holmium yang lasers that have been studied include the contact device that is available originally from Summit, although they dropped their PMA, and one that is investigated in Europe. That is the Technomed device. And the non-contact technology in the holmium is of course the Sunrise PMA we are presenting today.

Now the Summit contact hand held probe is a non-simultaneous delivery where you basically march around the cornea with a probe, and it's highly surgeon-dependent. That contact approach was abandoned due to irregular astigmatism and regression. I'm just bringing that up, because I want to distinguish our technology and our approach from that approach.

Some other specifics other than the fact that it's contact and non-contact is the fact that there is simultaneous delivery with the Sunrise, and the treatment parameters are very different. Summit uses 15 hertz. Sunrise uses 5 hertz. The number of pulses delivered in the Summit approach were 25 as opposed to 7. So that the overall energy delivered to the cornea was actually very high with the Summit approach, as compared to a relatively modest amounts with the Sunrise approach.

In the preclinical and clinical evaluation of the Sunrise device, a number of different ring parameters were evaluated. One, two, and three rings were looked at. The inner ring diameter was evaluated, ranging from 5.0 to 6.5 millimeters. And the orientations of various rings, whether they were staggered, one relative to the other, or radially aligned.

As a result of all these preclinical and clinical studies the optimal ring parameter selected for this FDA trial were two rings at the 6.0 and 7.0 millimeter zones, radially aligned. And these were selected to maximize outcomes, and also to maximize the size of the central untreated zone of the cornea.

This is the appearance of a patient immediately after treatment, and that just shows you the orientation of the spots in these two rings at 6.0 and 7.0 millimeters.

On your left you see a picture of the device. This is the actual laser in this box here, connected to the slit lamp delivery system by a fiber optic cable. Both the surgeon and the patient are seated at the slit lamp delivery system. The patient fixates at a central target, and there are eight tracer helium neon beams that represent each of the holmium beams, and these are centered around the patient's entrance pupil. So centration is very simple and

very predictable.

The treatment technique involves eight spots simultaneously delivered at 6.0 millimeters, and then a second ring is delivered at 7.0 millimeters. The spot size is about 600 microns. And we use seven pulses, and since this device works at 5 hertz, it represents 1.4 seconds per ring.

This short video will demonstrate the procedure that is used in the FDA trials. The additional equipment that is needed is obviously very simple: some preparacaine(?), eye pads, a lip speculum, and a timer. A drop of preparacaine is administered, and we then wait three minutes. A second drop is administered, again waiting an additional three minutes for it to absorb. Finally, a third drop is administered.

We wait five minutes, during which the fellow eye is patched to insure that there is no cross fixation. A lid speculum is inserted to prevent blinking during the procedure. And then the approach that we are going to recommend for labeling is to allow the tear film to dry naturally for three minutes. The laser energy is absorbed by the tear film, and we would like to have it dry completely by the time of the treatment.

The final instructions are given to the patient

with regard to fixation of the target while the lid speculum is in place. The laser is then prepared by setting the energy, as you see circled in yellow. The number of pulses is set at seven. Then the remainder of the laser is arranged, set a 6.0 millimeters. The orientation of the beams is established. One can insure that all the beams are in fact fully activated.

The final instructions are given to the patient. The final review of all laser parameters. The laser is activated. Then by stepping on the foot pedal one delivers the first ring of treatment, as you will see in the video in just a moment. You can see the helium neon tracer beams. I'm sorry those aren't real clear, but you will see them a little bit better on the slit lamp view through the camera.

That was the first ring that was treated. It's just that fast. Then the rings are adjusted from the 6.0 millimeter to the 7.0 millimeter diameter, again staying along the same radial alignment. The second ring is then treated. That concludes the treatment of the second ring.

The patient then sits back from the slit lamp. The lid speculum is removed, antibiotic drops are administered, and instructions for post-operative care are given.

This is a patient pre-operatively and immediately

post-operatively. You can see the whitening of the epithelium that takes place. In addition, there is haze in the stroma that has a conical shape that extends to approximately three-quarters depth. For the treatment parameters in this study, this is the appearance at one month. The spots are fairly faint. It varies from patient to patient obviously, but they are certainly relatively subtle.

At six months, again you can just see them with a broad beam illumination. Certainly you can readily see them with the other sclerotic scatter or retinal illumination. They have never been noticed by patients, or we have not had patient complaints relating to these, and they certainly are not visible to the naked eye after the first day or so.

This is an elevation map that tries to show the effect of the laser on corneal curvature. This is pre-operatively. At some point post-operatively you can see on a difference map that there is peripheral depression that is created along with the central elevation. If we then translate these elevation data into a corneal power map, in other words reflecting corneal curvature data, again pre-operatively, post-operatively you can see the nice large zone of correction that is generated here, which we think is in contradistinct. You can see the difference map, again,

the large central zone of steepening that is generated by the treatment.

On your left you see an anterior elevation map of laser thermal keratoplasty. And you can see that there typically is a smaller zone in patients that have undergone hyperopic LASIK. This study began with a feasibility study conducted in 1992 on non-sighted eyes by Peter McDonald. Then in 1993, the Phase IIA was begun of 28 eyes using different treatment parameters than we used in the subsequent trials. The expanded IIA was begun in April 1996, and we went into Phase III in November of 1997.

As will be pointed out by Dr. Stulting in his talk, the first group of patients in this expanded IIA study had a different drying technique used. And we initially thought that they would have the same results, but we subsequently began to see that these patients were undercorrected. So from about this point hence, we went back actually to the drying technique that was used in Phase IIA, and that's the drying technique that we think has produced the best results.

In a meeting with FDA in June 1998, we talked with them about our criteria for submitting the PMA. These criteria were generated. When stability was achieved in the accordance with the October 1996 FDA guidance, the PMA could

be submitted. That guidance indicated that 95 percent of eyes had to have a change in refraction of less than or equal to 1 diopter, 2 visits, 3 months apart. We had to have at least 300 cases at that stability endpoint, which turned out to be 6 months.

It was felt that 300 cases were certainly sufficient to detect less than a 1 percent incidence of complications, and more than sufficient for the efficacy endpoints. They also wanted to see 100 cases at one year following treatment.

If you look at what our data are, in December 1998 we submitted a PMA with 345 eyes, and 123 in a year. But actually, we had a 90 day update in March, and then in response to FDA questions in June, we now have at six months, which we believe is our stability endpoint, 596 eyes, 436 at 12 months, and 144 at 18 months.

If we use the FDA definition of accountability as circulated in the draft guidance document regarding accountability, we have excellent accountability, as you will see. I hope that's not one thing we will be discussing this afternoon also; 97 percent at one month, but basically 92 percent at six months, 86 percent at 12 months, and even 82 percent, even in excess of 80 percent at 18 months.

The investigational sites included: myself, Drs.

Alan Aker, Sandra Belmont, David Brown, Dan Durrie, Paul Ernest, Howard Fine, David Hardten, his partner Dick Lindstrom, Modest Trap, Peter McDonald, and Robert Gale Martin. So you can see we had an excellent group of investigators, who are highly respected ophthalmologists.

The indications for use in this study were unilateral or bilateral hyperopia +0.75 to +2.50, with 3/4 of a diopter refractive cylinder or less. Patient should be 40 years of age or older; 656 eyes were treated under this algorithm in which basically the only variable was laser energy, but the number of applications, spot placement, and pulse frequency was not varied. Again, the only other variation, as I mentioned, was that the first 46 eyes in that expanded Phase IIA had a different drying technique, which as we will point out, led to early undercorrections in these patient, and late undercorrections as well.

The pulse energy was varied based on the pretreatment manifest of refractive spherical equivalent ranging from 228 to 256 mJs.

Let's look at the safety. According to the October 1996 guidance the safety criteria include: loss of best spectacle corrected visual acuity of greater than 2 lines must less than 5 percent; vision less than 20/40 must be less than 1 percent; induced manifest refractive

astigmatism greater than two diopters should be less than 5 percent; and adverse events should be less than 1 percent per event.

If we looked at best spectacle corrected visual acuity, you can see a smattering of eyes on the plus side, and we have a small number of eyes on the minus side, and this is at six months. Specifically, we have 2.3 percent of eyes that lost two lines of vision. That represents 13 eyes, and because we used EDTRS charts, 11 of those 13 eyes lost vision from 20 over 12.5 to 20/20. The other patient was 20/25, another one was 20/32. So basically, they all retained excellent vision, although within the strict criteria of two lines, they certainly meet that criterion.

Of these patients, this represents two patients that lost more than two lines, and let's look at those in closer detail. One was a 60 year old patient that was 20/20 before treatment, but developed an age-related cataract at six months after the treatment, and his vision dropped to 20/40.

The only patient that could be considered attributable to the actual laser treatment is a patient who was 20/10 and at three months he was 20/13, but he dropped three lines to 20/20 at six months, but he was back to 20/13 at 12 months. So we don't really feel that there were any

patients who had any laser-induced loss of vision in excess of two lines. We believe that the preservation of best spectacle corrected visual acuity is unparalleled compared to other refractive surgical procedures, especially those for the treatment of hyperopia, or including those.

Adverse events include one patient with unresolved differential diagnosis of chronic retinoschisis, which is retinal detachment, whose vision was 20/25 uncorrected at one year. A 71 year old who developed a cataract at 12 months, and again the vision dropped in this patient to 20/50. It's hard to really relate any of these again to the laser treatment itself.

The FDA medical officer's review stated that "no laser related adverse events were reported during this investigation." Obviously, we are well below the 1 percent target per event.

If we look at other complications, you can again see these are really negligible. Some small comments about foreign body sensation, 0.2 percent at three and six months. Pain at 0.3 percent at three months. And again to quote the medical officer's review, "The only complications noted at six months or later post-treatment was mild foreign body sensation in a small number of patients. This generally consisted of mild itchy, scratchy feeling, requiring

artificial tears," not altogether surprising in a prediopic(?) population.

If we look at the incidence of induced manifest cylinder, and this is one of the questions for panel discussion, I think question three, the FDA criterion for this is cylinder greater than 2 diopters must be less than 5 percent. At six months we had 0.8 percent, and at 12 months, 0.2 percent. So obviously it was way, way below the FDA target.

If we expand that a little bit and look at greater than equal to 2 diopters, we're still well below that 5 percent threshold. If we extend that a little bit farther and look at greater than 1 or great than or equal to 1 diopter, the only time that we remain above the 5 percent threshold is just for the greater than or equal to 1 diopter.

But if we look here at 18 months, we have your four eyes that have more than a diopter of induced cylinder at 18 months. Actually, every one of these eyes had excellent correct acuity. There was no loss of best corrected acuity, and three of these four eyes had 20/32 uncorrected vision. So we don't think that induced cylinder is an issue. I think we have demonstrated not only the safety, but preservation of excellent vision.

I'd like to make a few more comments about induced cylinder, because the precision of measurement for this parameter has not really been established. There are no reported data in the literature that we could find for induced cylinder of greater than a diopter, or greater than or equal to a diopter for other refractor procedures. Nor are there criteria for cylinder change of these magnitudes in the FDA guidance document, and it's not a criterion that has been used to judge previous refractive devices.

If we think about the measurement issues here, for a manifest refraction, the accepted standard deviation for measurement error is around a half diopter, so that gives you about 95 percent plus or minus 1. Cylinder measurement is generally assumed to have a higher standard deviation.

Assuming a standard deviation, however, of a half diopter, remember we are starting with patients that don't have cylinder. Up to 5 percent of induced cylinder greater than a diopter could be attributable to measurement error alone, which we think could be another compounding factor in these patients at 12 and 18 months. However, bottom line, I think we have met the FDA criteria. There is no loss of vision in these patients with regard to this issue.

So reviewing again the safety criteria, loss of greater than two lines, vision worse than 20/40, induced

cylinder greater than 2 diopters. We are way, way, way below the FDA criteria.

Another question for panel discussion related to double vision. We gave patients a questionnaire, and they could check if they had double vision. We decided to contact those patient that had checked that they had double vision either at 6 months or 12 months after surgery, because again this relates to topics that have already been discussed before the panel today in the public session, and with regard to the LASIK submission.

What we found is certainly the majority of patients had none. But those that we contacted by phone, if we combine all these groups, 95 percent of the patients either did not initially check that box, or those that did, they said it wasn't worse than pre-op or it wasn't bothersome.

Now we were unable to contact 3 percent of the patients, but 2 percent of the patients said yes, they still had double vision when contacted. But if we looked at the data, none of them had loss of best spectacle acuity, all of them had good uncorrected acuity, and all of them indicated that they had good patient satisfaction. So we don't think that that this is an issue of any sort that we need to worry about.

If we again look at another issue in question four, light sensitivity and photophobia, often and always, if they checked that box, we did the same thing. Those that checked the box, we called them, and we had an independent person call both that group and this group. Again, we had 95 percent of the patients who either didn't check the box, or indicated it wasn't worse than pre-op, or wasn't bothersome. Again, interestingly there was a different group largely, but 3 percent couldn't be contacted.

But of the 2 percent that said they still had light sensitivity and photophobia, 1.8 percent said they were still satisfied with the procedure. Interestingly, the only patient who said that she wasn't satisfied, was upset because she lost the near vision that she had gained early in the post-operative period, and then had lost that.

Now if look at safety and think about alternative procedures, I think we are all aware of the potential complications of the microkeratome. These are just a few. Some of these are mild. Some of these are obviously more severe, corneal perforation, retinal hemorrhage, optic nerve injury. There are a whole array of flap complications that can be induced with hyperopic procedures involving a microkeratome. I think that we don't really need to dwell on these, except to remember them in this discussion.

If we look at post-operative complications, dry eye, lasekias(?), epithelial defects, yes; epithelial ingrowth under the flap, yes; irregular astigmatism, yes in LASIK. I'm going to put minimal under Sunrise, simply because if you define irregular astigmatism as loss of best spectacle corrected acuity, or visually symptomatic problems, then I would say we have none, but I think if you did topographic analysis, you would certainly find some small amounts of it. But we think it's well below the clinical threshold.

Loss of best spectacle corrected visual acuity, certainly with LASIK and none with Sunrise. I say none, because the only patients we had were two cataracts, and one patient that dropped transiently to 20/20 and went back to 20/13.

Other LASIK problems, infection, interface inflammation, stromal melts, vascular occlusions, macular hemorrhage, retinal hemorrhage, and it is certainly worth pointing out that LASIK as a procedure involves cutting through the visual axis, and the Sunrise procedure is obviously conducted well outside it.

I would close on this issue of safety by posing the question, is there any other refractive surgical procedure that has this outstanding safety profile?

I'm going to turn the podium over to Dr. Stulting, and thank you for your attention.

DR. STULTING: Thank you, Dr. Koch. I'm Doyle Stulting. I'm professor of ophthalmology at Emory University. I'm a paid consultant for Sunrise Technologies. My involvement with them began about a year ago when they asked me to review this data and help them prepare it for submission. I told them that I had not had any experience with this, and I am not one of the investigators. I have, however, subsequently used the instrument outside of the United States, and examined patients post-operatively. So I do have some experience with the device.

My job today is to discuss with you efficacy, patient satisfaction, and stability. This slide shows the FDA guidance criteria for effectiveness: 85 percent of eyes should have 20/40 or better uncorrected acuity; 75 percent should be within 1 diopter of the attempted correction; 50 percent within a half a diopter.

And the definition for stability is that 95 percent of eyes have a manifest refraction spherical equivalent within 1 diopter measured on two visits that are at least three months apart.

Dr. Koch emphasized that the drying technique that was used in this investigation in fact changed during the

study. During Phase IIA, which did not contribute any of the data that are in the cohort submitted for analysis today, a three minute drying time was utilized. This in fact was the one that was seen in the video.

When the expanded Phase IIA was begun, that is, the investigation that provided the data for you today, the investigators decided that it would appropriate to change the drying time, and in fact the protocol was changed so that a 30 second drying time was used, and this was followed by a damp WeckCel sponge wipe of the cornea.

After the initial patients were treated, it became apparent to the investigators that the outcomes were not as good as those that they were used to seeing in Phase IIA. So they were analyzed at that time, and it turns out that these patients indeed were being undercorrected. As a result, the initial drying technique was reinstated, and continued for the remainder of this study.

When the data were originally submitted to the FDA, concerns were raised about the poolability of this early treatment group. A preliminary analysis was performed at that time with the available data, looking at outcomes three and six months post-operatively. These appeared to be poolable.

As you saw in the slides that Dr. Koch presented,

a considerable amount of data has become available since the initial submission. Now additional analysis clearly demonstrate that these data are not poolable with the remainder of cases. Moreover, the inclusion of these data actually artificially skews the outcomes to make the outcomes look much worse than they really are. This is particularly the case with late outcomes.

The analysis of the earliest cases, that is those with the longest follow-up show that there were fewer eyes that were overcorrected by a diopter or more early on at one month. There were fewer within a half a diopter of intended correction at 12 months. There were differences in uncorrected visual acuities at 1 month and 12 months. And these eyes were consistently more hyperopic, with statistical significance being reached at one week, one month, three months, and 18 months. So there was a statistically significant difference in at least nine separate efficacy parameters shown in this slide.

The sponsors properly concluded that the early cases had been undertreated, leading to less early overcorrection, better early uncorrected visual acuity, but poorer late results when stability had been reached. It is therefore, not statistically valid to pool the early cases with the remainder of the cohort.

Let me show you just two slides to give you a good feeling for what's going on with these early cases. This slide shows the percentage of cases contributed to the original cohort at each time period. The blue line shows the contribution of the first 50 cases, while the red line shows the contribution of the cohort without the 50 cases included.

You can see here that early on in the consistent 12 month cohort, the first 50 cases contributes about 10 percent of the outcome measures. At 18 and 24 months, however, the early cases in fact contribute an increasing portion of the outcome measures. So that at 24 months, these early case contribute the majority of the outcomes.

So that if you are having poorer outcomes in these 50 cases as a result of a technique change, what you can expect is that the data will look worse at these time points out here, than it did in the early time points simply because these cases contributed a disproportionately larger amount to the cohort.

Let's look for example at the percentage of eyes that achieved 20/20 or better visual acuity. Here the green line presents the original cohort submitted to the panel for review. You can see here that there is an unquestionable fall off in the percentage of eyes that has 20/20 visual

acuity from 12 to 24 months.

Let's look at the eyes that were treated with the new drying technique, the first 50 cases. What we see is that in fact at three months had a higher proportion 20/20 or better outcomes. This is the case, because they didn't get the overshoot that is necessary in order for optimal outcomes to be produced. From 12 months on, as these eyes became a larger and larger portion of the data pool, you can see that the outcomes fall off.

The red line shows the outcomes of the cohort minus the first 50 cases. Here the percentage of eyes that achieved 20/20 or better acuity is essentially stable throughout the observation period, out to 24 months. So all efficacy analyses that are presented here, will be presented using the consistent 12 month cohort, without the first 50 cases in here. It's 357, still exceeding the number that is felt to be necessary for this analysis.

We think it's important to note that data presentations that include the first 50 eyes simply do not reflect the results that are obtained with the recommended drying technique that was used for the remainder of cases, and that is intended to be used when the device was approved.

Let's look then at efficacy. This slide shows

uncorrected visual acuity at six months after treatment; 88 percent of eyes were 20/40 or better; 78 percent, 20/30 or better; 59 percent, 20/25 or better; and 40 percent, 20/20 or better.

This slide shows the percentage of eyes that are 20/20 or better as a function of time after treatment. You can see that 85 percent of eyes are 20/40 or better at 12 months, and 86 percent at 18 months. Thus, the FDA target value of 85 percent is exceeded at each of these examination points. Notice as well the 95 percent confidence interval here for the last three measures. These confidence intervals overlap, indicating that there is no significant change in the percent of eyes achieving 20/40 or better with time beyond six months.

The average visual acuities obtained at 6 months, 12 months, and 18 months are another indicator of the stability of the outcome that is obtained with the procedure. These numbers are 20/27, 20/27, and 20/28. In fact, the disparity in uncorrected visual acuities between 6 and 18 months is 0.9 EDTRS letters. Clearly, within measurement error, and clearly below the level of clinical significance.

This slide shows the percentage of eyes that are 20/20 or better with time after surgery. There is no FDA

guidance target for this number, but we show it anyway. You can see that 40 percent of eyes are 20/20 or better at 6 months; 38 percent of eyes are 20/20 or better at 12 months; and 37 percent of eyes are 20/20 or better at 18 months. Once again, the 94 percent confidence intervals overlap at six months and beyond, indicating that there is no statistically significant difference in these outcomes.

So in summary, the distance uncorrected visual acuity is stable within statistical limits between 6 and 18 months after surgery. Only a very small, amounting to a 2-3 percent non-statistically significant change is seen in the percent of cases seeing 20/20 and 20/40 or better at these time points. At 6, 12, and 18 months post-treatment the percent of cases that is 20/40 or better meets or exceeds the FDA guidance target value of 85 percent.

Ninety percent of eyes six months post-operatively were within 1 diopter of the target manifest refraction spherical equivalent. This exceeds the FDA target value of 75 percent.

Looking at this number as a function of time, we see that 90 percent of eyes were within 1 diopter of the intended correction at six months; 84 percent at 12 months; and 80 percent at 18 months. Notice the expanded confidence interval here, and the fact that the confidence intervals

overlap. There is no statistical difference among these measurements. Again, all of them exceed the FDA target value of 75 percent.

This slide shows predictability; the number of eyes within a half a diopter of intended correction as a function of time after surgery. Sixty-six percent of eyes were within a half diopter at six months; 58 percent at 12 months; and 48 percent at 18 months. The FDA target value of 50 percent is met at all intervals except this one, where the eyes in this study fall 2 percent below the target value. The confidence interval is wider here, because there are fewer eyes to examine, but it still incorporates the 50 percent value. So in summary, this device meets FDA effectiveness criteria.

Let's talk for a moment about patient satisfaction. As you know, a survey was sent to these patients initially. To clarify and understand the answers, the sponsor called all patients who reported any dissatisfaction with the procedure at 6 or 12 months after treatment where the reason was not clearly delineated in their initial responses to clarify the data as much as possible.

Here are the results: 87 percent of these patients were satisfied; 3 percent could not be contacted.

Let's take a look at the 10 percent who were identified as being dissatisfied. One of them was the patient that Dr. Koch described with the cataract. One of them was dissatisfied because of a slight overcorrection.

Three patients actually had good distance vision, and were pleased with the good distance vision. Their dissatisfaction was based on the fact that they liked the near vision that they got when they were initially overcorrected immediately post-operatively. The bulk of the patients were dissatisfied simply because of undercorrection. This protocol did not permit retreatments, so these patients could not be treated.

International experience, however, at this point indicates that retreatments are not only possible, but are effective. And Dr. Anschuetz is here today to answer questions if you have any of him.

But remember that this PMA is being sent to you as a single treatment modality. No enhancements were permitted, and yet the satisfaction rate is still quite high. More importantly, no patient mentioned visual symptoms such as glare, halos, difficulties driving at night, or diplopia as a cause of dissatisfaction.

This point is especially pertinent because of the comments made in the public session this morning, and

because of the comments made in the presentation earlier today. It is clear that this agency must look at outcome measures other than Snellen visual acuity to assess the safety and efficacy of devices.

And I say this again for emphasis, because it's very important. No patient mentioned visual symptoms such as glare, halos, or difficulties driving at night or diplopia as a cause of dissatisfaction.

An effort was also made to understand why fellow eyes were not treated. The sponsor contacted all patients who did not wish treatment during the study for their fellow eyes to determine the reason that they didn't want treatment. Ninety-six percent of these patients fell into one of the three categories indicated on the slide. Either when they were contacted, they had actually already had the other eye treated, or they desired to have the treatment, having originally postponed the treatment for personal reasons, for scheduling reasons, or because the protocol simply didn't allow treatment of their second eye.

The third group of patients answered no to this question for reasons that were totally unrelated to negative outcomes of the primary LTK, that is, they were not candidates. They had monovision, and like it. And the one patient who had the cataract was also in this group.

Therefore, only 4 percent of patients in this study chose no fellow eye treatment for any reason due to the first eye outcome.

Now the obvious reason to have refractive surgery is to get rid of glasses and contact lenses. This was accomplished in 88 percent of eyes in this study, and remember that additional repeated treatments were not allowed.

Let's talk for a moment about stability, and I'm going to dwell on this, because there were concerns that were raised about this in the early panel reviews. The first thing that I want to say is that the criterion that has traditionally been applied to stability is that eyes be within 1 diopter manifest refracted spherical equivalent from one visit to a next, with those visits being at least three months apart.

The target value is that 95 percent of eyes fulfill this criteria. At the agency's request, multiple analyses for stability were performed at the time of the original submission. This bar represents the outcomes from the 6 month consistent cohort, from the 12 month consistent cohort, from the 18 month consistent cohort, and from the entire cohort. All of these subgroups fulfill the FDA requirement for stability at 6 months.

Additional questions, however, were raised about the stability of this procedure following six months. This slide shows the post-operative spherical equivalent manifest refraction on the vertical axis as a function of time after treatment on the horizontal axis going out to two years. You can see that there is some change here with a tendency toward a more hyperopic refraction. The rate of change is not the same on the first part of this curve as it is at the last part of this curve.

This graph shows you the rate of change, so that the first point represents the rate of change from one week to one month; the second one from one month to three months, and so on. This graph shows pair-wise data, so that every eye that has available data at one week and one month is included in this measurement, and so on. So we're getting as much data as we can, and as many analyses as we can.

It is apparent that there is a rapid phase here where the loss of correction occurs at a fairly rapid rate, and then this is followed by a slower change here. I emphasize now this is rate of change, not the actual manifest spherical equivalent. So when this line reaches zero, there is statistically and mathematically zero change.

This is a much more detailed and sophisticated analysis than has ever been presented before to my knowledge.

Those points from four months onward bear a linear relationship to the months after treatment. This is the rate of change in diopters. This is the time after surgery. There is a tight linear regression fit as you can see from the line, with an R squared value 0.98, and P value of 0.008.

If this line is extrapolated to the horizontal axis, the intercept is at 26.3 months. In fact, if you look at the eyes with the current drying technique, the intercept is at 20.5 months. This is another mathematical and statistical proof of long-term stability beyond the FDA criteria.

I call to your attention the absolute value shown on the horizontal scale here. This is one-tenth of a diopter per month at the top of the scale. This is one-hundred of a diopter per month at the bottom of the scale. At the last time these eyes were examined the change rate was 0.02 diopters per month.

It is clearly incorrect to conclude that the spherical equivalent continues to change with time, and to extrapolate the rate of change from the last examination indefinitely. In fact, the data clearly show that with the current drying technique there is 0 rate of change of by the most statistically appropriate and stringent analysis that

we can perform at 20-21 months.

Step back from this a moment, however, and realize that these data meet the FDA criterion at six months. The additional analyses that I have shown you here are simply additional data that are provided because of the original comments that were received.

The sponsor in fact met with FDA personnel during the development of the PMA to determine what rate of change would be acceptable. The guidance that were received at that time was that about 0.3 diopters per three months would be appropriate and within the range of acceptability, although a lower value would be nice to see. It was suggested that 0.3 diopter mean change would not by itself be a reason to disapprove a PMA, although the change rate might be appropriately reflected in the labeling.

The Sunrise LTK exceeds the 0.1 diopter per month criterion at all time points. In fact, it drops from 0.09 diopters per month at 3-6 months, to two-hundredths of a diopter per month between 12-18. This is the figure that you need to remember.

During the preparation of this PMA, we were curious academically about the refractor results of treatment for hyperopia. The data on this slide are shown to you not for direct comparison to the LTK data, but

because we believe that the decisions that are made today should be made with the full knowledge of existing treatments and existing publicly available literature, which this represents.

What you can see here by simply eyeballing the slide is that for all of these treatment modalities the post-treatment spherical equivalent continues to drift toward hyperopia for all time points and for all studies. These represent Excimer laser treatments.

The details of these publicly available treatments are shown in this slide. As you can see there are five different laser manufacturers. It includes seven studies for PRK and two for LASIK. It includes follow-up intervals that vary from 6 months to 24 months. The drift rate per month at the last available measurement interval varies from a low of 0.03 diopters per month, to a high of 0.36 diopters per month.

So looking at this data on hyperopic refractive procedures, it appears that the magnitude of change is similar regardless of the manufacturer or laser type. In fact, the similarity in drift rates between these studies may in part be due to physiologic or measurement changes.

In conclusion, the PMA cohort results that have been presented today, and that you have in your hands,

surpass or meet all safety, stability, and effectiveness criteria for refractive lasers. Given the extraordinary safety profile, the efficacy and stability, this is a technology that should be available to physicians and patients in the United States, as an option for refractive surgery.

Thank you.

DR. MC CULLEY: Does that conclude the sponsor's presentation? Thank you for a well done presentation.

I believe there is a request by FDA that we break now for set up for your AV needs. So we will take a 10 minute break.

[Brief recess.]

DR. MC CULLEY: Before we begin, I just want to let everyone be aware that we are following the new approach of having one of the primary reviewers serve as scribe to list all the areas of concern and questions so that there is someone other than me trying to keep up with the listing of issues. Dr. Michael Grimmert has been asked to do that for this PMA.

Prior to resuming with the PMA, Dr. Rosenthal, you had an announcement?

DR. ROSENTHAL: May I make two comments before Dr. Eydelman starts her presentation? The first comment has to

do with the guidance document to which all sponsors are referring. That guidance document, which was dated October 1996, is for low to moderate myopia up to -7 diopters. There is no guidance document yet that has been established by the agency, and in fact when we discussed the issues with the panel, I think they did not advise any levels for other indications. They suggested we keep that document in place. But it is still the document for low myopia to -7.

The second issue has to do with comparison data which the current sponsors have presented. Dr. Stulting prefaced his remarks by saying that the data is presented for general knowledge only. You are not allowed to use it as comparative data.

I think the other issue I must point out is that it is not data that has been vetted by the agency. So whether or not it is accurate, I just don't know, and the agency doesn't know. It is not a study that the agency has overseen. And certainly the publications are not publications that the agency has condoned. So I want you to be aware of that. Although it is correct for him to present it as background or informational knowledge to the panel to help make the decision, you cannot make a direct comparison. The PMA must stand on its own.

DR. MC CULLEY: Dr. Pulido?

DR. PULIDO: Your, honor, a point of order. I believe that the sponsors -- we should be able to question the sponsors before the FDA gives their presentation about it.

DR. MC CULLEY: That's correct. We'll bring them back. But if you think there are issues now that we should query them about before FDA is given the floor, we can do that. The sponsor will be back for the opportunity query.

MS. THORNTON: Is Nancy Puhouski(?) here? She needs to address this.

DR. MC CULLEY: Shuffle time guys. Sorry. I'm going to ask the FDA to depart the table, and the sponsor to return for us to query. That's my second big mistake for today. That's your first one.

Does panel have questions for the sponsor? You better -- Dr. Pulido.

DR. PULIDO: Just one quick question. In volume number five you showed a beautiful regression analysis, figure three, and you had shown it up there as well. I actually preferred the one that you showed now, because it first showed one steeper curve, and then a less steep subsequent curve.

If you do the integral of that curve, or basically just take the area underneath that curve, that will be your

total dioptric change over that time period. Did you do that analysis?

DR. KOCH: No, we did not. It's a good idea. We didn't do it.

DR. PULIDO: I think it's very important and very telling. Maybe later on we'll talk about that.

DR. MC CULLEY: Are there any other questions?
Dr. Sugar?

DR. SUGAR: Do you have any data on the rate of change or rate of regression with age? That is for a population that was treated at age 40 versus a population treated at age 50, was the rate of change different?

DR. KOCH: No, we don't have those data. We could look at that. We didn't, as I remember, find that age is much of a factor in terms of outcomes, either in terms of amount of correction given endpoints or uncorrected acuities. But we did not do specifically a regression rate in accordance with age.

DR. GRIMMETT: On the regression line that was presented in Dr. Stulting's slides, as well as just was referenced in volume 5, page 8, figure 3, to the best of my knowledge those data arrive from a not continuous cohort of patients. I think it is derived from volume 3, table 41a. Is that correct? Are those not a continuous cohort of

patients?

DR. STULTING: Those are pair-wise analyses of the follow-up for the entire cohort. So that if a patient had data available on two adjacent examinations, the data from that patient were included, even if we didn't have data available for another. Because what we were interested in looking at here was the change from one examination to another, not the overall change from the beginning of the study to the end. So it would be appropriate to include patients who have adjacent examinations, even if that's all the data that are available on that patient.

DR. GRIMMETT: And those data did not then exclude the first 50, is that correct?

DR. STULTING: The original graph that I showed you, and this one include even the first 50 eyes, because we didn't know -- the hypothesis is that those eyes are basically undercorrected. But once they are treated, whatever effect that they get is going to follow more or less the same course as the other eye. So to be complete, this includes all of the eyes, even the first 50. If you examine the cohort without the first 50, the X intercept occurs even earlier than it does with this cohort at about 20 months instead of 27.

DR. MACSAI: According to the protocol, the

sponsors performed cycloplegic refractions pre-operatively, at 6, 12, and 18 and 24 months. Have you provided that data?

DR. KOCH: Yes, we have. They actually show -- presumably because this is a pre-hyperopic population, that there is no more than 0.09 difference throughout a mean between the manifest and the cycloplegic.

DR. MACSAI: But have you done regression analysis, refractive drift analysis on that data?

DR. KOCH: No, we have not. We don't think it's a concern because of the similarity of the numbers.

DR. STULTING: Dr. McCulley, I've done a little math, and I think I can answer Dr. Pulido's question. Your question was what's the area under this curve in figure 3. You can compute that pretty quickly, because the horizontal number is 27 months, the vertical number is about one-tenth, so it's 2.7 diopters. You have to divide that in two, because it's a triangle. So the entire dioptric change represented by this graph is 1.35 diopters.

DR. PULIDO: Correct, so that's what I had gotten from that one. But if you add the other steeper curve, it is closer to 1.5. So over the time period, I calculate there is about on average 1.5 dioptric change in these patients. So I think that's important, and your data should

have been analyzed to look at that, because it's there from the data and important data considering what the average was that we first started with, number one.

Number two, I would like to say on the other hand, you have wonderful accountability, and I think that is very important.

DR. KOCH: Thank you.

DR. MC CULLEY: Other questions for the sponsor?

DR. MATOBA: I'd like you to clarify this information. This is table 3 from the medical officer's review regarding demographics. In the subset of 260 patients who mastered a questionnaire, 16.9 percent did not wear glasses or contact lenses pre-op. I was wondering how those patients entered into this study, and what their expectations were, and what the criteria would be for satisfaction?

DR. KOCH: That was full-time spectacle wear.

DR. MATOBA: No, didn't wear glasses or contact lenses.

DR. KOCH: The question worded to the patient was full-time, as in the actual questionnaire. That's a good question. We were permitted to enter patients whose uncorrected acuities were actually better than 20/40, because it's hard to recruit patients who are +3/4 and +1,

whose uncorrected acuity sometimes are worse than 20/40. So that's how we were able to fill in some of those low numbers in terms of the level of hyperopia. And some of those patients do many thing without glasses.

DR. GRIMMETT: Dr. Stulting presented a slide that showed statistical analyses between the earliest cases treated and the later cases treated. Some of those, I believe are in volume 2, amendment 6, but I don't think all of them are. Were some of those data new on your slide versus what was in the materials?

DR. STULTING: You're asking for the slide that had the nine P values on it?

DR. GRIMMETT: Yes. I believe the data on the earliest cases, at least that I'm aware of by reviewing the materials show I believe two statistical analyses in amendment 6, volume 2. And a lot of those data, do they appear in the materials we received?

DR. STULTING: You had analyses early on for the original data that showed poolability. You should have received this information that was presented today. Perhaps not?

DR. GRIMMETT: I'm not aware of it. On the earliest cases treated that you presented the slides on, at least in amendment 6, volume 2, they were comparing for

example, the first 77 eyes versus the remaining 521. Were any of those data that you presented specific to the first 50? Were the first 50 looked at compared to the rest? Or it should be the first 46, because that's where the drying changes. I assumed you rounded it off, is how you came up with 50.

DR. STULTING: Yes, that's right.

DR. GRIMMETT: Were they referable to the first 50?

DR. STULTING: The data actually that were on that slide were obtained by analyzing the people who had late follow-up. So I think you are correct in what you are saying. Yes, those were the people that contributed to the late follow-up.

DR. SANDERS: Donald Sanders, a consultant for Sunrise. I'm not sure that you have seen the information, but the mean spherical equivalent between the two groups at one week, one month, I believe three months, and 18 months are significantly different from them with the later data. I have to look, but I'm not that that's in the submission you have seen. There was the 50.

DR. MC CULLEY: Does the FDA have that data? I think this is a procedural point, is it not, Dr. Rosenthal? We need to know if the FDA has received that data for

evaluation. If they have not, my understanding is that it's not submissible.

DR. KOCH: I believe we have some of the comparisons there, but I believe that we don't have all of the ones, as Dr. Grimmert pointed out.

DR. MC CULLEY: But there is a procedural point with this that I think we are bound to go by. And that is that you cannot submit data for consideration that has not been submitted to the FDA for their evaluation prior to meeting.

DR. STULTING: Okay, I'll respond to that. On page 4 and page 5 of the amendment 6, you will see accuracy of manifest refraction at 1 month and spherical equivalents at 12 months, spherical equivalent at 1 month, and 20/25 or better at 1 month, and low hyperopia group. That is on page 6; 20/20 or better at 12 months, and the low hyperopia group. That's on page 6. Then 20/20 or better at 1 month, in the moderate hyperopia group. That's on page 7. So that's the bulk of the data.

It's actually kind of unusual. Ordinarily, the sponsor is fighting for poolability. Here we are admitting non-poolability, and saying that these eyes were treated with a different technique, and we don't think that your decision ought to be based on that.

DR. MC CULLEY: This is a procedural point.

DR. STULTING: The answer to your question is that they are found on those pages that I just cited.

DR. MC CULLEY: Dr. Grimmatt, does that satisfy your question?

DR. GRIMMETT: Yes, I need to look at your slide again, but yes, that satisfies my question. Thank you.

DR. MC CULLEY: Other questions of panel members for our sponsor? Dr. Macsai?

DR. MACSAI: If you could just save me a little time. Can you tell me what page I would look on for the cycloplegic refraction outcomes data on the group -50? Which of these volumes and which page?

DR. SANDERS: That was a very recent request by the FDA to provide a table on cycloplegic refraction. We're trying to pull it right now.

DR. MC CULLEY: Has the FDA received that?

MS. THORNTON: Yes, it's in your handout. It's probably the next to the last page in your notebook under the PMA number.

DR. ROSENTHAL: Mr. Chairman, may I also comment that the information that Dr. Grimmatt was questioning was submitted.

DR. MC CULLEY: So we're still looking for the

cycloplegic -- have you found it? Dr. Pulido?

DR. PULIDO: While they are looking for the cycloplegic, maybe you could help me, because this is going to come up later. If the mean pre-op was 1.69 diopters hyperopia, and if the area to that curve is around somewhere between 1.35 and 1.5 diopters, then at 26 months the patient is back to +1.5 diopters, the average patient.

DR. KOCH: That's very important, and that sort of came out in our presentation. We looked for an early overcorrection. In other words, we looked for initial correction of -1, -1 1/4 because of the fact that these patients do drift back, and we do need that area under the curve hopefully to occur below the level of ametropia. So that is intended, and that's an understood part of the procedure. And I think you heard that actually some of our patient dissatisfaction data occurred with patients that lost that initial near acuity.

So there is an initial overcorrection that we seek in order for the patient to drift back to what we will be ametropia plus a quarter or whatever, in that range. That's how the procedure is intended to work.

Did that answer your question?

DR. PULIDO: No, because you have lost 1.5 diopters by the end. So if you are starting at 1.69, if you

lost that 1.5, you are back to --

DR. KOCH: But that curve starts at four months.

DR. STULTING: You're not getting the whole curve.

And it doesn't make sense to me to do the analysis you are talking about. The curve that I showed you is the first derivative of the refraction with time. That is based on the original raw data. If you all want to know is what the total change is in the population, you ought to go back to the original raw data, instead of reintegrating a curve that doesn't include all of the post-operative points.

DR. PULIDO: Well, you are the ones that submitted the curve.

DR. STULTING: Yes, but it wasn't for the purpose that you are using it for. It was for the purpose of analyzing the rate of change, and how the rate of change relates to time after surgery. It wasn't designed to determine what the total change was, or the residual fraction was.

DR. MC CULLEY: Other questions for our sponsor? Have you found what you are looking for, Marian?

DR. MACSAI: He let me look at those. It was not in my packet.

DR. MC CULLEY: You have it? You found it?

DR. MACSAI: Dr. Waxler(?), what you showed me was

a single page like this. It just compares the pre-op mean, manifest refractive spherical equivalent and cycloplegic refractive spherical equivalent at 6 months and 12 months. It doesn't tell me anything about the data on that.

DR. MC CULLEY: Do you still have a question then?

DR. MACSAI: I'll address it in my review.

DR. MC CULLEY: Okay. Any other questions for sponsor?

DR. MATOBA: Did you check intraocular pressure immediate after the procedure? It seems to me that if there is uniform energy to shrink collagen there, you might have an increase in IOP short-term.

DR. KOCH: We did not. We checked them early post-operatively, and we've done that in earlier studies, checked them as early as a day, but not immediately. We actually in some patients found lower pressure, almost as if it was pulling on the trabecular mesh work.

DR. MC CULLEY: At what time point?

DR. KOCH: In the first few weeks, but it went ahead.

DR. MC CULLEY: So you don't know what the shrinkage, whether you crowded and shot the pressure up?

DR. KOCH: No, we don't. That inconceivable to me that that would happen.

DR. HIGGINBOTHAM: Well, since the door was open, I'll walk in. Did you do baseline gonioscopy and follow-up gonioscopy considering these people are hyperopic and older than 40?

DR. KOCH: No, we did not, although I don't think any of us would have enrolled patients that have clinically narrow looking angles, just on clinical judgment.

DR. HIGGINBOTHAM: The gonioscopy was done?

DR. KOCH: Was not done.

DR. SANDERS: Can I address that issue of glaucoma? As you recall, we had those elevation maps that actually quantitate the amount of elevation and depression of the cornea. And we're dealing on the order of possibly a depression, which would be a tightening, of approximately 20-25 microns. That's on the anterior surface of the cornea. When you look at the posterior surface, there is virtually no movement of the posterior surface.

So given that, it's highly unlikely that -- and these have been done fairly acutely, within hours of the procedure -- so it's highly unlikely that those would have an effect on intraocular pressure.

DR. MC CULLEY: Any other questions? We'll excuse the sponsor now. Now the FDA is invited back to the table.

Agenda Item: FDA Presentation of PMA P980051

DR. WAXLER: Well, good afternoon. I have the pleasure of introducing Dr. Everette Beers, who will be giving a brief description of the PMA. I'm still chief of the Diagnostic and Devices Branch.

DR. BEERS: Thanks, Morris. Good afternoon. My name is Everette Beers. I'm the team leader for the Sunrise Technologies P980051. This is a holmium YAG laser for laser thermal keratoplasty. The application was filed December 14, 1998. The sponsor is requesting approval for a laser thermal keratoplasty for the correction of hyperopia between 0.75 and 2.5 diopters.

The primary panel reviewers for this application are Dr. Michael Grimmett and Dr. Marian Macsai. I wanted to thank, or at least recognize the FDA team that has been evaluating this PMA, and also to recognize Marsha Nicholas, who was the team leader for the clinical study portion of this. Engineering and physics were Dr. Bruce Drum, Capt. Robert Faaland, and Dr. Woody Ediger; for statistics, Ms. Phyllis Silverman; from GMPs, Ms. Mary-Lou David; for patient information labeling, Ms. Paula Silberger, and Ms. Carol Clayton; and for bioresearch monitoring, Ms. Pam Reynolds; and for software review, Mr. Joseph Jorgens.

At this time I would like to introduce the clinical reviewer for this application, Dr. Malvina

Eydelman.

DR. EYDELMAN: Good afternoon. I would like to preface my talk today with the fact that I have not seen a final copy of slides of the panel presentation slides today. Therefore, please forgive any redundancies that might be contained in my presentation.

The Hyperion LTK System, as you heard, is a non-contact holmium YAG laser that delivers laser energy to cornea via a procedure known as laser thermal keratoplasty, or LTK. This device is the first non-Excimer refractive laser to be presented for panel consideration. Currently, we do not have a guidance specific to this technology.

The Hyperion LTK system is intended for patients with unilateral or bilateral hyperopia in the range of 0.75 to 2.5 diopter spherical equivalent, with less than or equal 0.75 diopters of pre-existing cylinder. It is intended for patients who are 40 years of age or older.

PMA cohorts analyzed in the submission have undergone several revisions. I would like, therefore, to define all the cohorts at the beginning of this presentation for clarification purposes. PMA cohort analyzed in amendment 2 incorporated all qualified eyes treated as 3/12/99. Analysis of this cohort was the basis of my written review and primary panel mail out. The sponsor

subsequently began to refer to this cohort as "original." For the sake of clarity, I will adopt this terminology.

Subsequent to the primary mail out, in an attempt to answer questions raised in my review, as well as questions from the primary panel reviewers, the sponsor submitted three additional amendments. In my presentation today I have incorporated data in all the amendments received by FDA as of today.

In order to provide the agency and the panel with the most up-to-date information, the sponsor has updated the PMA data set, and submitted some of the analysis to FDA on June 28. This cohort is being referred to as the "updated" cohort. The sponsor has also submitted some analysis on the updated cohort following removal of the first 50 cases. This cohort is referred to as the "updated minus 50."

Two types of pretreatment drying techniques, as you heard, were utilized during this study. The first 46 eyes enrolled were prepared for treatment by placing the lip speculum, allowing the eye to air dry for 60-90 seconds, and then wiping the cornea with a moist WeckCel sponge. The remaining eyes enrolled were prepared for treatment using modified drying technique. The lid speculum was put in place, and the eye was allowed to air dry for three minutes, and the WeckCel sponge was not used.

As of amendment 2, sponsor believe that the first 46 eyes could be poolable with the rest of the cohort. Sponsor states that following a further update of the database, however, substantial differences were found, and that currently they believe that these eyes should not be poolable. The FDA statistician agrees that the first 46 eyes can be analyzed separately.

The sponsor has settled on excluding the first 50 eyes, because "this is a round number, and most of them received the old drying technique." Sponsor believes that inclusion of the first four cases with the current drying technique did not change the outcome. Most likely sponsor is correct in this assumption. We have not yet, however, received data to validate this conclusion.

I would like to point out the magnitude of the increase in the eyes analyzed in the updated versus original cohort. While the number of eyes at 6 months essentially remained the same, the numbers analyzed at 12, 18, and 24 months almost doubled. Updated cohort had also significantly better accountability at 18 and 24 months intervals as compared to the original.

In order to determine the appropriate point of refractive stability after treatment with this new device, sponsor was asked to present data for all available eyes,

i.e., pair-wise sequential visits, and 6, 12, and 18 months consistent cohorts. That is, eyes that were examined at each exam.

Analysis of the stability of the original 12 month consistent cohort is presented in this slide. This analysis of the original cohort eyes that had data for 1 week, 1, 3, 6, and 12 months exams. While between 3 and 6 months, 95 percent of all eyes had a chance of MRSE less than or equal to 1 diopter. And this number remained at 94 percent between 6 and 12 months.

Looking at the mean rate of change per months, it is decreasing from 1 diopter per month between 3 and 6 months, and 0.06 diopters between 6 and 12 months.

If we look at the comparable analysis for the 18 months cohort, we can see that between 12 and 18 months the mean rate of change is 0.05 diopters. These two slides mean that between 3 and 6 months the mean rate of change would be equivalent to 1.2 diopters per year, decreasing to 0.72 diopters per year between 6 and 12 months, and 0.6 diopters between 12 and 18 months. But certainly as Dr. Stulting pointed out, it is not a constant change.

In the latest amendments sponsor provided stability analysis utilizing pair-wise sequential visits only for the updated cohort. I have compared it to the

equivalent analysis of the original cohort in these slides.

As one can see, there is a slight decrease in the mean rate of change per month beyond the six months interval. Of most interest, however, is the outcome for 18 to 24 months time frame.

Due to low N, stability analysis was not assessed between 18 and 24 months in the original cohort. As one can see in the updated cohort, 90.7 percent of eyes experienced change in the MRSE less than or equal to 1 diopter in this time frame, while the mean rate of change per month was calculated to be 0.02 diopters.

Data in the PMA was also asked to be stratified according to the degree of preoperative hyperopia. A low hyperopia was defined from 0.75 diopters up to 2, and the moderate hyperopia was defined as 2-2.5 diopters. Stability analysis stratified by diopter group show a trend for moderate hyperopes to have slightly lower percentage of eyes, with less than or equal to 1 diopter between consecutive visits, and higher mean rate of change per month. The panel will be asked to incorporate all this data in their determination of the appropriate stability time point.

Analysis of the predictability of the manifest refraction in the original cohort shows the decrease in

accuracy with time. The sponsor has recalculated the predictability for all three cohorts, as you can see in these slides. As you can see, the accuracy within 0.5 diopters decreases from 65 percent at 6 months to 11 percent at 24 months in the original cohort.

While 6 and 12 month outcomes are almost the same for all three cohorts, the outcomes at 18 and 24 months are improved significantly in updated and updated minus 50 cohorts. Accuracy within 1 diopter shows a similar reduction with time, and once again this reduction is less in the updated and updated minus 50 cohorts.

Data in these slides point to regression as the probable cause of decrease in predictability of MRSE with time. In the original cohort, percentage of eyes undercorrected by greater than +1 diopter increased from 10 percent at 6 months, to 56 percent at 24 months. Updated cohort data is rather similar, with an increase from 10.3 percent at 6 months, to 45.8 percent at 24 months. Similarly, undercorrection by greater than +2 diopters shows an increase with time in all cohorts.

Once again, the sponsor was asked to stratify the predictability of manifest refraction by the level of hyperopia. A similar analysis was carried out for the updated minus 50 cohort, but only for the subcohort of the

eyes seen at all exams through month 12, i.e., 12 months consistent cohort. Even though this analysis shows continued decrease in percentage of predictability within 0.5 diopters with time, the decrease appears to be smaller than in the original cohort.

Predictability within one diopter showed a decrease, mostly of 18 and 24 months in the original cohort.

As you can see once more, the decrease is less in the updated minus 50 cohort. One more time just to point out, this analysis also carried out only for the 12 months consistent cohort.

We can see that decrease in predictability in stratified analysis once again points to regressions as the cause. Undercorrection is smaller, but still present in the updated minus 50 cohort.

Moderate hyperopia predictability analysis of the original cohort showed a rather dramatic decrease in accuracy, within 0.5 diopter with time. Even though once again the updated minus 50 cohorts analysis is somewhat better, please note that at 18 months only 25 percent of moderate hyperopes achieved accuracy within plus or minus 0.5 diopter. Also, please note that due to the very low number of eyes available at 24 months, we do not really know the outcomes at this time point.

Accuracy of manifest refraction within 1 diopter decreases to 36 percent for moderate hyperopes in the original cohort at 18 months. Fifty-eight point one percent of the updated minus 50 consistent 12 months cohort achieved accuracy of refraction within one diopter at 18 months.

As you can see, the increase in undercorrection greater than 1 diopter with time in moderate hyperopes is rather large. The updated minus 50 cohort once again shows somewhat less of a change. Note, however, that even in this cohort the percentage of eyes undercorrected by greater than 1 diopter more than doubles between 6 and 18 months.

It is of special interest to analyze the percentage of eyes that end up undercorrected by greater than 2 diopters among those that started with preoperative refraction between +2 and +2.5 diopters. At 18 months, 6.5 percent of the updated minus 50, 12 months consistent cohort were undercorrected by greater than +2 diopters.

Panel members are being asked to incorporate all these outcomes in their recommendations this device's predictability of correction of refractive error.

While only 0.2 percent of eyes had UCVA of 20 or 25 or better preoperatively in this study, 38.3 percent of the original cohort was able to see 20/20 or better at 6 months, obviously, quite a good improvement. The percentage

of eyes that maintained that level of UCVA, however, seems to have decreased with time. Here I have plotted the outcomes of UCVA of 20/20 or better for all three cohorts.

In white you can see the curve for the original cohort, yellow plots the outcome of the updated cohort, and green, the updated minus 50 cohort. In your interpretation of the 24 months outcomes, please consider the fact that there were only 13 eyes available for analysis in the updated minus 50 cohort; 18 for the original; and 48 for the updated cohorts.

While UCVA of 20/40 or better appeared to decrease with time in the original cohort, updated and updated minus 50 cohorts have almost insignificant changes through the 18 months. Once again, the 24 months data had difficulty to give too much weight to due to a rather small N.

UCVA data on our request was also stratified by degree of preoperative hyperopia. The sponsor has provided an updated, stratified analysis of UCVA only for updated minus 50, 12 months consistent cohort. There appears to be an insignificant drop with time in this cohort. For moderate hyperopes, however, there seems to be definite decrease in UCVA with time in both cohorts.

The 24 months data for UCVA for moderate hyperopia is based on total N of 2 for the updated minus 50 cohort,

and an N of 5 for the original. Thus, once again, accuracy is quite a question.

UCVA of 20/40 or better for low hyperopes showed a minimum decrease with time. For moderate hyperopes, however, there is a definite drop in the percentage of eyes achieving 20/40 or better with time. Panel members will be asked to comment on the acceptability of UCVA outcomes at all time points for this device.

Another issue that I would address today is the cylinder induction associated with this device. At 6 months there appears to be a significant percentage of eyes with magnitude greater than or equal 1 diopter. Please observe quite a significant reduction in this percentage between 6 and 12 months in the original and updated cohorts. The percentage of eyes with cylinder greater than 1 diopter is significantly smaller than that seen for increase greater than or equal to 1 diopter. However, one can still see it in 9 percent of those original and updated cohorts.

Only about 2 percent of eyes experience an increase in cylinder magnitude of greater than or equal to 2 diopters, and less than 1 percent experienced greater than 2 diopter cylinder increase at any time point.

Vector analysis was performed to evaluate the axis orientation at 6 months post-treatment for the cases among

the original cohort that had greater than 1 diopter of cylinder induction; 65.4 percent of these cases exhibited surgically induced cylinder in against the rule direction, and 32.7 percent had oblique induced cylinder.

Those cases who had an increase in post-treatment astigmatism of greater or equal to 1 diopter has significantly more pre-treatment hyperopia by an average of 0.12 diopters than those that did not. And also as expected, post-treatment UCVA was significantly worse in the increased astigmatism group.

Panel members will be asked to comment on their interpretation of the significant of the induced cylinder with this device.

According to the protocol, a patient questionnaire was administered in this study pre-operatively, and at 1, 6, 12, and 24 months post-operatively. Photophobia and double vision appeared to be the visual symptoms with the greatest change in the study. While pre-operative 0.7 percent of patients had mild, moderate, or marked photophobia, 6.9 percent experienced this level at 6 months, and 8.2 percent at 12 months. Double vision experienced often or always increased from 3.4 percent pre-op to 14 percent at 6 month and 12 months.

In order to better understand the significance of

the visual symptoms found to be of concern in the study, the sponsor attempted to contact by phone all patients who reported significant photophobia or double vision. At the time of the telephone questionnaire only 2 percent of patients continued to have bothersome photophobia, and 2 percent had bothersome light sensitivity. Unfortunately, from the sponsor's telephone questionnaire data, the post-operative time frame for resolution of symptoms is unclear.

Even though the sponsor did a lot of work to investigate the current status of patients' with special symptoms, they have not yet submitted updated patient questionnaire analysis. In light of almost doubling the number of eyes examined at 12 months in the updated cohort, and availability of 48 eyes at 24 months, an updated analysis of the patient questionnaire might reveal additional important information.

Panel members will be asked as to their recommendation of the necessity for the analysis of this data prior to an approvability decision.

Spherical equivalent at the 180 day post-treatment exam was analyzed as a continuous variable as the function of various baseline factors. Increased corneal curvature was found to be directly correlated with the amount of reduction in hyperopia with each diopter that associated

with 0.05 diopter increased refractive change.

Thus, with all other variables being equal a patient with a corneal curvature of 46 diopters would expect to have 0.2 diopters more effect than a patient with a 42 diopter corneal curvature given the same treatment.

Increased age was also directly correlated with increased effect, with all the patients having 0.018 diopter reduction in hyperopia per year of increasing age. Thus with all other variables being equal, a 60 year old patient could expect to have a 0.36 diopter more effect than a 40 year old given the same treatment.

Caucasian patients had 0.262 diopter less refractive change compared to non-Caucasian patients. Thus, with all other variables being equal, Caucasian patients would expect about a quarter diopter less than the non-Caucasians.

Each unit of baseline spherical equivalent was associated with an increase in the 180 day spherical equivalent by 0.64 diopters. This correlates well the observation that slight undercorrection occurred at the higher ranges of treatment.

I bring all of these to your attention since all of these associations will be reflected in the final decision of the patient.

I do want to highlight some of the other safety factors associated with this device. As you heard, analysis of the original cohort did reveal low loss of BSCVA. There no laser-related adverse events, and minimal complications. Furthermore, the endothelial cell analysis performed in this study did not show any significant changes.

Taking all of these factors into consideration, I would like to go ahead and pose the questions.

1. Which cohort -- original, updated, or updated minus 50 -- do you believe to be the most appropriate for assessment of safety and efficacy of this device?

2a. Has adequate refractive stability been demonstrated with this device by six months?

2b. Based on the refractive stability presented in this PMA, is the current follow-up of eyes treated sufficiently to provide reasonable assurance of safety and effectiveness of this device?

3. The predictability of manifest refraction and the uncorrected visual acuity results decrease between 6 and 18 months. Does this raise concerns about treatment efficacy?

4. At 6 months post-treatment, 18 percent of all eyes examined had greater than or equal 1 diopter increase in cylinder. Most induced cylinder axes were in against-

the-rule and oblique directions. Does this raise any concerns?

5a. Visual symptoms data reveal photophobia and double vision to be the symptoms with greatest change from pre-operative levels. Do increases in these visual symptoms constitute a safety concern?

5b. Is analysis of the updated patient questionnaire necessary prior to making a recommendation regarding approvability of this device?

6. Do the safety and effectiveness outcomes stratified by diopter of preoperative hyperopia +0.75 to +1.99 diopter and +2.00 to +2.50 diopter support approval for the full range of hyperopia of +.075 to +2.50 diopters of spherical equivalent?

7. What are your recommendations for labeling regarding:

- a. potential regression;
- b. cylinder induction, and
- c. visual symptoms?

Do you have any additional labeling recommendations?

This completes my presentation. Thank you for your attention.

DR. MC CULLEY: Thank you. Are there questions

for the FDA from the panel members at this point?

DR. HIGGINBOTHAM: Malvina, I was struck by the differences between the original group versus the updated group in terms of the drying technique. Recognizing again that this is an over 40 age group, I wonder if there was any difference in gender considering the prevalence of dryness in women post-menopausal versus men. Did you see any evidence of that in the data?

DR. EYDELMAN: I did not see any analysis to that.

DR. MC CULLEY: You didn't see any analysis to that, so you can't answer the question?

DR. EYDELMAN: Correct.

DR. WANG: I've been trying to think about difference between the original and the updated, the minus the 50. If it's a mere drying effect, it should add a constant amount to the correction, just parallel shift perhaps in time by a constant amount. I don't know whether anybody performed that analysis, you or the sponsor, by taking into account that the two groups still coincide pretty well if the matter of not drying is just a constant amount on the correction.

DR. EYDELMAN: I agree from the slide that Dr. Stulting showed there was a different rate of regression of effect.

DR. WANG: Then you should find the amount of correction by a constant amount. The two curves should coincide, because if hydration only results in the undercorrection, that should be just a parallel shift. It should not change the nature of stability of this procedure whether or not this 50 is included or not.

DR. EYDELMAN: Perhaps you can ask this of the sponsors when they come back to the podium.

DR. MC CULLEY: Any other questions for FDA? Dr. Pulido?

DR. PULIDO: I just would like to commend Dr. Eydelman for a wonderful presentation.

DR. MC CULLEY: I think we all share in that.

DR. FERRIS: Malvina, I still don't understand why is it 46 or 50. Were there 46 people that didn't have drying, or were there 50?

DR. EYDELMAN: There were 46 that had the original drying technique. And in the original analysis these 46 were compared to the rest of the cohort and found to be poolable. Later on in the latest amendments received within the last two weeks or so, the updated cohort analysis was once again compared against the 50.

Now as I said, sponsor claims that the 46 to 50 was just a rounding effect, and that these four eyes

shouldn't make any difference, but we have not really seen any data to that effect. That was a bit confusing, and that's why I had those slides. Perhaps you want me to go back.

DR. FERRIS: No, I'm still confused. I'll just remain confused. Maybe later the sponsor will unconfuse me.

DR. ROSENTHAL: May I suggest you ask that of the sponsor?

DR. MC CULLEY: Dr. Grimmett, you had a question for FDA?

DR. GRIMMETT: She clarified it, thank you.

DR. MC CULLEY: Any other questions, points of clarification for the FDA? Seeing none, we will go to the primary reviews. The first primary review would be by Dr. Marian Macsai.

**Agenda Item: Primary Panel Review of PMA P980051
- Dr. Marian Macsai**

DR. MACSAI: Before proceeding with my review of PMA 980051, I would like to commend Dr. Eydelman on her outstanding review, and commiserate with her for the need for rapid turnover in analysis of complicated data provided by the sponsor in rapid sequence. The sponsors presented to us tremendous data in voluminous quantities, and they also should be commended for the organization of that data and

presentation.

Before proceeding with the details of my review, I would like to define some relevant terms for panel members and the audience. First slide. Hyperopia exists when the resting, non-accommodating power of the eye is too weak.

Next slide. Accommodation is the ability to increase the refractive power of the eye beyond its static resting power. Accommodation is measured in diopters. At age 40 the average person has 6 diopters of accommodation. These numbers are removed from the book, "Optics for Clinicians," by Mel Rubin, the most recent edition. At age 44, the average person has 4.5 diopters of accommodation, and at 48 years of age the average person has 3 diopters of accommodation. By 52 years of age, the average person has 2.5 diopters of accommodation. As we age, our accommodation decreases.

Third slide. Cycloplegia is the temporary paralysis of accommodation or paralysis of the surrounding muscle activity, and can be temporary when done pharmacologically.

Next slide. By definition, absolute hyperopia cannot be overcome by accommodation. And the total hyperopia of a patient can only be elicited by cycloplegia.

Latent hyperopia can only be uncovered by cycloplegia. For

the ophthalmologists in the audience and on the panel, of course this is the undercorrected hyperope, the patient that drives many physicians a little bit crazy by their astronomic complaints, which are vague, and frequently related to their undercorrected hyperopia, and with age, their inability to accommodate, to overcome it.

Next slide. Manifest hyperopia is the portion of total hyperopia accepted by the patient without cycloplegia.

That includes the facultative hyperopia or portion of total hyperopia which a patient can overcome with accommodation.

We know that accommodation plays a significant role in hyperopia, and that accommodation decreases with age.

Therefore, the manifest hyperopia, the facultative hyperopia, and the latent hyperopia in the patient will all change with age.

These changes are continuing in patients 40 years of age or older. Therefore, studies in hyperopia must compare the total hyperopia in a patient pre-operatively with the total hyperopia post-operatively to determine what effect a refractive procedure has in a hyperopic patient if that patient is going to be measured on two time points between which they age.

Next slide. Efficacy can only be established by comparison of the total hyperopia at two separate post-

operative time points. The sponsor has measured the cycloplegic refraction (total hyperopia) and treated patients at the pre-operative and the post-operative visits 6, 12, 18, and 24 months, according to their protocol.

Within our handouts there is one page that addresses cycloplegic refraction. In it, it shows at 6 months the mean cycloplegic refraction spherical equivalent is 0.27, however, at 12 months this increases to 0.57.

Next slide, please. Refractive stability is critical in analysis of this PMA. We are talking about the treatment of patients from +0.75 diopters to +2.50 diopters hyperopia pre-op such that analysis based on measurements of 2 diopters would be significant adverse events. So we must look at the data on a much different scale when we are talking about treating such a small amount of refractive error.

If we are talking about refractive stability, the sponsors have calculated refractive stability of LTK, and demonstrated a progressive decrease in the mean rate of manifest refractive spherical equivalent changes, with the change of 1.09 diopters per year between 3 and 6 months, 0.7 diopters per year between 6 and 12 months, 0.5 diopters per year between 12 and 18 months, and 0.5 diopters per year between 18 and 24 months.

In volume four, the sponsor suggests the refractive change may not be related to changes in corneal topography, but perhaps secondary to articular changes or changes in accommodative amplitude. If the original measurements used to treat patients with LTK were based on cycloplegic refractions, and accommodative amplitude had been measured pre-operatively, then this hypothesis would not be speculation.

In fact, the pre-operative measurement of accommodative amplitude in the hyperopic patient population over 40 years of age would be critical in interpreting post-operative results and stability, as would the pre-operative and post-operative cycloplegic refraction. In this way, the sponsor will be able to demonstrate the true effect of the procedure, and whether or not the natural changes in accommodative amplitude experienced in the over 40 population play a role.

The sponsor has provided a comparison of the results of three data sets as alluded to and clearly demonstrated by Dr. Eydelman. The original PMA cohort, the recent updated data, and then the updated data without the first 50 cases. The reason for exclusion of the first 50 cases was a difference in drying technique on the first 46 patients, which had a significant effect on data when

analyzed by the primary reviewers and FDA medical officer.

Table 1, as you see, demonstrates the percentage of eyes undercorrected by greater than 1 diopters, combining primary and fellow eyes. Percentage of eyes undercorrected by greater than 1 diopter at 6 months in all three groups is 10 percent. This increases to between 31 and 56 percent by 24 months in each of the groups.

Next slide. When you look at the patients examined through the 12 month visit, again, segregating the patients based on the grouping of original, updated, updated minus 50, again the same trend is seen of an increase in undercorrection with time.

Next slide. This same trend to an increase in undercorrection over time is seen in the patients with a 18 month follow-up, however, it's not as rapid a drop off between 18 and 24 months, but the number of patients is very low at the 24 month visit.

Here we have the data from volume five, in which the sponsors have segregated patients treated for low and moderate hyperopia to see what is the percentage of patients undercorrected by greater than +1 diopters. Again, in the low hyperopic group at 6 months this is 3 percent, however, it increases dramatically to 22 percent by 24 months. In the moderate hyperopes, 19 percent are undercorrected by

greater than +1 diopters at 6 months, and this increases to 50 percent by 24 months, however, the numbers at 24 months are probably too small.

Next slide. If you look at the hyperopes and try and see how close they are to where they were supposed to be, or in other words, the plus or minus 1 diopter manifest spherical equivalent. In the low hyperopes the data looks okay out to 18 months, but again, it falls off at 24 months, which may be attributable to the small numbers. In the moderate hyperopes there is significant fall off between the 6 and 24 month time period.

In this slide the percentage of patients in the three groups that have a visual acuity of greater than 20/40 is seen. At 6 months, approximately 87 percent of all eyes treated had a visual acuity of 20/40. By 24 months, this number decreases to between 61 and 70 percent, depending on how you segregate out patients with the drying technique or without.

Next slide. The same trend is seen in patients with 12 months follow-up, with a significant fall off at 24 months, but note that the Ns are rather small. In the all eyes, minus the first 50, the N is 11.

Next slide. And this trend is seen again, but not as clearly with all eyes who are followed-up to 18 months.

Next slide. Now we are looking at the uncorrected visual acuity of greater than 20/20, all eyes available. Now these measurements again are made by allowing the patients to accommodate to the best of their ability. With these measurements it appears that between 38 and 39 percent of patients in each group have an uncorrected visual acuity of 20/20 at 6 months. But by 24 months this percentage has dropped to somewhere between 11 to 31 percent. Thirty-one percent in the bottom right-hand square is 4 out of 13 patients. At 6 months there were 548 patients, and at 24 months we have data on 15.

All nine tables that I have just shown you demonstrate a refractive drift with an increase in the percentage of patients that are undercorrected by greater than +1 diopters from 6 to 24 months. A decrease in percentage of patients with uncorrected visual acuities of greater than or equal to 20/40 between 6 and 24 months, and a decrease in the percentage of patients with an uncorrected visual acuity of greater than 20/20 from 6 to 24 months.

Regarding the induction of cylinder of greater than 1 diopter of astigmatism, in my opinion this issue remains one of safety. The sponsors quoted the guidance document from 1996 intended for low to moderate myopia, stating the safety guideline of patients with greater than 2

diopters of induced astigmatism should be less than 5 percent of subjects.

However, if a device is treating patients with between +0.75 and +2.50 diopters of hyperopia, then it is reasonable to look at induction of greater than +1 diopters of astigmatism as a safety variable. The data quoted by the sponsor demonstrates greater than +1 diopter of astigmatism induced in 8 percent of patients at 12 months, 10 percent of patients 18 months, and 11 percent of patients at 24 months.

It is disconcerting that this induced astigmatism appears to be increasing in time. Yet the sponsor states the astigmatism tends to resolve with time. Now this irregular or induced astigmatism could very easily be the cause of patients' complaints.

The sponsors made an excellent effort to contact by telephone all the patients who complained of double vision. When asked again by telephone, less patients complained of diplopia. However, corneal topography, refractions to detect astigmatism and/or hard contact lens over refractions to determine irregular astigmatism, were not included in this addendum.

Lastly, I'd like to address retreatments. In volume four the sponsor stated that retreatment questionnaires were sent to eight centers demonstrating

greater than 3,000 primary LTKs performed with between 9-30 percent requiring retreatment, and 7-20 percent retreated with LTK, with 50-70 percent success rate with retreatment.

The data is given only on 27 eyes from one center, and 11 from another.

In summary, to determine the safety and efficacy of the treatment of hyperopia with LTK, follow-up of the total hyperopia in patients to the 24 month visit will clearly supply data to establish whether or not there is a refractive drift, and whether or not there is a safety issue with induced astigmatism. Further analysis of this data at 24 months is recommended.

DR. MC CULLEY: Thank you, Dr. Macsai. Dr. Grimmatt.

**Agenda Item: Primary Panel Review of PMA P980051
- Dr. Michael Grimmatt**

DR. GRIMMATT: My detailed safety and efficacy comments can be found in the written documents I have previously supplied, dated 24 July. This presentation will summarize some of the highlights, but it's not intended as a comprehensive substitute.

I apologize for being redundant. I had not seen some of the presentations prior to this panel.

We have talked about the three cohorts. The

manufacturer over the last month has presented data on three separate cohorts requiring three separate data analyses. The original cohort has a large drop off in eyes after the six month interval, shown in the blue, which drops off markedly in the later time intervals.

I agree with the manufacturer in volume one, page 198 when they state, "The decreasing number of eyes available for follow-up on beyond six months precludes any conclusion from being reached beyond this time point. Data at these outer post-treatment visits represents the initialized treated and the learning curve issue for a small number of eyes available, and may not be representative of the overall study cohort or subsets."

The updated cohort provided shows a doubling of numbers at the 12, 18, and 24 months interval. We have approximately two-thirds of eyes in at 12 months. We have already seen the accountability data. At 18 months there is 80 percent of eyes missing, and at 24 months there is 92 percent of eyes missing.

For the updated minus 50, there is a serious data limitation. At 24 months there are only 13 eyes available in the updated minus 50 data set. Overall for these longer time intervals we can look for a trend, but we cannot generate firm conclusions based on these data.

Regarding the exclusion of the first 50 cases, we discussed the drying technique changed after case 46. I just found out today why it was rounded to 50. In volume one, appendix G, the first 46 weren't considered doable because there was no statistically significant difference on several outcome variables to include distance and near uncorrected visual acuity, best spectacle corrected visual acuity, as well as those remaining plus or minus 1 diopter from intended.

I have learned today that there was statistical analysis regarding the first 50 to the rest of the updated data, however, these data have not been supplied to me for analysis, so I cannot make comment whether it is appropriate to exclude or include these 50.

The data down at the bottom regarding that there are less overcorrections in the earlier treated eyes is seen in amendment 6, volume 2, under tab 4. That is one feature I believe that was on Dr. Stulting's slide.

I'll talk very briefly about a few safety issues. Regarding best spectacle corrected visual acuity of loss greater than 2 lines, it approximates 3 percent after month 6. The higher rate of best spectacle corrected visual acuity loss one month suggests early post-operative irregular astigmatism subsequently improves with time. All

eyes were 20/40 or better in six months, as previously noted. While not insignificant, a 3 percent rate likely meets the standard of reasonable safety.

There was approximately a five fold increase in frequency of diplopia at 6 months, suggesting induced regular astigmatism, irregular astigmatism and/or other higher order visual aberrations. By phone survey the sponsor has now presented data showing a decrease in these symptoms of diplopia.

Photophobia increased approximately 10 fold, considering mild, moderate, or severe photophobia at 6 and 12 months. The updated data by phone survey additionally showed a decrease.

Comparing treated versus untreated eyes, there was approximately a four fold increase in sensitivity to light between the eyes show in blue; a two and a half fold increase in night difficulty between the eyes, shown in pink; and approximately a three fold increase in glare between the eyes. Regarding all these symptoms concerning photophobia and night vision problems, diplopia and glare, I would simply recommend that the labeling should reflect the potential for increased visual symptoms consonant with the most updated data that we have.

The major limitation of this study to my mind is

regarding the stability of the refractive effect. The major study limitation that is a confounding factor for the entire study, as Dr. Macsai has already alluded to, is that there is no cycloplegic data that is available for my review. The table that was discussed today was not provided to me. I did not have the opportunity to review any cycloplegic data on this cohort.

If the patients are hyperopic, residual accommodative reserve can be expected to skew the results. Hence, for all uncorrected visual acuity tables, expect skewing of the uncorrected visual acuity data toward better visual outcomes. Additionally, the refraction accuracy may also be altered.

Looking at astigmatism magnitude greater than a diopter of approximately 1 in 5 had astigmatism induction greater than or equal to a diopter at 6 months. Fortunately, this does decrease with time and direction to light. By 12 months it drops to 8 percent, and gradually climbs to 11 percent in the original cohort. In the updated cohort, in the pink, it decreases with time.

We like that it decreased, however, the mere fact the astigmatism induction is shifting points to refractive instability of the procedure. I would rather see it stable at some level, whatever level that might be.

Seventeen eyes were evaluated for astigmatism axes. For ten eyes against-the-rule, 6 months later and at the 12 month interval, there were only 4 eyes against the rule. At the 6 months interval for eyes with oblique astigmatism, of six eyes there was only one remaining oblique. One eye remained at the 6 and 12 month intervals with visible astigmatism.

Hence, the astigmatism may shift against the rule to oblique or vice versa. The mere fact that there is an astigmatism directional shifts with time, granted it's a small subset, it does suggest refractive instability. I was unable to locate updated data in this regard.

Looking at the uncorrected visual acuity for the moderate hyperopes -- and I apologize that this is redundance -- some of the tables that have been presented reflect these data. Looking at those greater than 20/40 in the original cohort, we see it decreases over time. We realize the limitations over longer time intervals. Those of greater than 20/32 decrease in time. Those greater than 20/20 decrease over time.

Showing the updated minus 50 cohort for completeness, although as I stated, I have not seen the statistical analysis that warrants the appropriateness of doing this technique. Those remaining with 20/32 or better

decrease over time. Those remaining with 20/20 or better decrease in time, with an isolated data point at 18 months, and those remaining greater than 20/40 did not decrease, however, taken together the progressive declines in uncorrected visual acuity suggests regression of the refractory effects.

Looking at predictability, those remaining plus or minus a half or plus or minus 1 diopter from intended in the original cohort, we see decreases in those remaining plus or minus 1, decreases in those remaining plus or minus a half.

The updated minus 50 again for completeness, with a weak data point out here in the 24 months, we do see a small decrease in those remaining plus or minus 1, and a similar trend in those remaining plus or minus a half. Taken together the declining predictability with time also suggests refractive instability.

Looking at the moderate hyperopes with regard to predictability, those remaining plus or minus a half or plus or minus 1 diopter from intended, generally decreased with time in the original cohort. The updated minus 50 also shows a trend, although not as marked. We also see decreases for plus or minus a half. For moderate hyperopes the declining predictability also suggests refractive instability.

For all eyes looking at predictability plus or minus a half diopter from intended, all three cohorts showed declining predictability over time. No matter how you slice it, they all go down. The updated minus 50 does not decline as dramatically however, and realize the weakness again of the later time intervals. These declining predictability with time suggest refractive instability.

Looking at the low hyperopes as a percentage of undercorrections, we see both for the original and the updated minus 50 cohort increasing undercorrections with time suggesting regression from refractive effect.

Similarly, for the moderate hyperopes we see increasing undercorrection with time to a whopping greater than 50 percent down here at the later time intervals, suggesting regression with refractive effect. Lumping all eyes together, no matter how you slice it, all three data sets show increasing undercorrections with time as a trend going upward. These also suggest regression from refractive effect.

This is not a consistent cohort of eyes. From the original cohort, the mean refraction changes from month 1 to month 18. It changes by approximately 1.5 diopters in the hyperopic correction. Interestingly, the change in the refraction almost agrees with the area of the curve that Dr.

Pulido pointed out earlier of 1.35. The increasing mean refractional time suggests refractive instability. The updated data mimics this curve, showing increasing refraction over time.

There is also a large continuous refractor shift between time intervals. This is the original cohort for a consistent cohort of 72 eyes at 18 months from table 50, volume 1, page 38. Between the 3 to 6 month intervals, 0.92 diopter per year shift, between 6 and 12 months it's a 0.76 diopter shift, from 12 to 18 months there's a 0.56 diopter per year shift.

I was unable to locate a consistent cohort in the updated data set from the material that was provided to me.

You have already seen the pair-wise data presented. This continuous refractive shift over time suggests a large percentage of the refraction in fact is temporary, and I interpret this as poor efficacy.

In summary, regarding refractive instability, the following features suggest: (1) refractive instability in this PMA of astigmatism magnitude shifts; (2) astigmatism axis shifts; (3) progressive declines in uncorrected visual acuity; (4) progressive declines in the proportion remaining plus or minus a half or plus or minus 1 diopter from intended; (5) progressive increase in uncorrections; (6)

progressive increase in the mean manifest refraction spherical equivalent; and (7) a continuous refractory shift between time intervals.

Taken together, since it can be reasonably construed that the average patient will want more than a temporary refractive effect, it is my firm opinion the PMA is not approvable since reasonable assurance has not been given that the device is effective under the conditions for use described, recommended, or suggested for the proposed labeling.

My recommendations would be to complete the data collection for longer time intervals; prepare a revised analyses for all of the outcome variables; and resubmit a revised PMA to the FDA at a future date for review. Perhaps if the refractive instability shift can be better nailed down at the later time intervals, appropriate labeling can properly advise patients as to what to expect regarding the seemingly temporary nature of this procedure.

Thank you all for your attention.

DR. MC CULLEY: Thank you, Dr. Grimmatt.

In terms of procedure now, the panel will begin its deliberation. But I have heard a sentiment, and then we will call FDA back and the sponsor back for closing comments. I heard a sentiment for a break. Is there a

sentiment for a break? Okay, there is enough of a sentiment for a break.

[Brief recess.]

DR. MC CULLEY: The panel will now begin its deliberation and discussion among ourselves of this PMA. We will then have the 30 minute open public hearing session, and then five minutes of FDA closing remarks, and then five minutes of sponsor closing comments.

So would the panel like to have open discussion at this point, or would you like to conduct the discussion using the mechanism of placing the questions that the FDA has up and answering them?

DR. SUGAR: I think some of this needs open discussion. This is different from the things we looked at before, at least in full panel. I think there have been some homework assignments on hyperopia, but not full panel reviews of hyperopia. We are starting with a population that has a mean refractive error of plus 1.69 diopters. So the criteria of stability being 1 diopter of change over any time interval, 1-3 months, 3-6 months, 6-12 months and so on, is not applicable. That is, that's too easy or too broad a criterion if you are starting out with 1.69 diopters and you stable can get 0.99 regression, that's not stable.

Likewise, predictability or accuracy plus or minus

1 diopter in 75 percent is not sufficient. So that everything we do with looking at this I think is sort of without precedent in terms of our previous activity. I think that there was a suggestion from the primary reviewer that they become appropriate, even though they would not have been appropriate for other modalities for other indications. That is hyperopia is different from myopia.

DR. PULIDO: Just a question for the panel. The one I had asked the sponsors, there was this change back towards pre-operative levels. They said this was normal hyperopic drift. I would like know if that truly is the natural history of hyperopes that they become more hyperopic over time.

DR. BULLIMORE: There is excellent published cross-sectional data on this from the Beaver Dam study and the Baltimore eye study. Both suggest that there is indeed a hyperopic shift that goes in the forties and the fifties population. In the sort of population that we are looking at here, I would guess that the change for the decade was somewhere on the order of 3/4 of a diopter per decade, so less than 0.1 per year, and less than 0.01 diopter per month.

We actually presented some data on this a couple of years ago, which is why I know the data. We had

longitudinal data, retrospective, and found similar results.

About a half a diopter shift for the decade in the hyperopic direction. So again, 0.05 per year, and way less than 0.01 diopters per month.

Personally, I don't believe that it's physiological.

DR. PULIDO: So the 1.35 diopters hyperopic shift over time, over 24 months would not --

DR. BULLIMORE: Over the course of the study I would imagine that less than 0.1, or at most 0.15 diopters was "physiological," maybe 10 percent of the total change.

DR. MC CULLEY: In your studies that have been done in your analysis of the others, how much of these is development of absolute hyperopia, and how much of it is our inability to compensate for refractive hyperopia?

DR. BULLIMORE: Data in these studies is largely collected in the same way as it was collected in this study.

DR. MC CULLEY: So there wasn't cycloplegic? So you really can't tell?

DR. BULLIMORE: We didn't have cycloplegic data. But one thing that is evident from the sponsor's data that they present, is that there is no systematic change over the study period between discrepancy cycloplegic and non-cycloplegic. I think there is a danger that we overstate

the cycloplegic issue.

DR. MC CULLEY: I heard concerns about the absence of cycloplegic data. Did I mis-hear, Dr. Grimmett?

DR. GRIMMETT: That was correct. I did not see any cycloplegic data materials provided to me, and I would have like to have seen them.

DR. WANG: I have actually two comments. One is in addition to the question with respect to guidance criteria for this type of correction, in addition to the lower magnitude of correction, I think the cornea, for some reason, is very reluctant to become more steepened. It doesn't mind to be flattened. That's the way a cornea likes to behave.

So I think in addition to the low magnitude correction, that we need more stringent criteria in stability follow-up. Also, the natural tendency, so to speak, that the cornea doesn't like to be steepened is also a reason to have more stringent criterion follow-up.

My second comment has to do with discussion of Dr. Pulido and Dr. Stulting. I did a calculation of the two graphs that they were mentioning. One is figure 3 and one is figure 4 of this blue, which 1 in 5. The figure 3 is the rate of change over time. Figure 4 is the hyperopic refraction over time.

You can integrate figure 3, and it is consistent with the results in figure 4. It is consistent in each figure, that there is about 1 diopter over 18 to 24 months hyperopic shift.

DR. ROSENTHAL: I just want to comment that the panel has in fact considered a hyperopic PMA for Excimer laser.

DR. PULIDO: I would like to say at that time we accepted the theory of hyperopic shift as physiological.

DR. MC CULLEY: Which Dr. Bullimore has stated as real. What was your assessment of the hyperopic shift in this relative to physiologic shift?

DR. BULLIMORE: It's not physiological. This is a genuine change, a genuine regression. And were I free to discuss other studies, I would say that was genuine regression as well. This is not a physiological effect.

DR. MC CULLEY: But we're sticking with this PMA.

DR. BULLIMORE: I think this is perhaps a little off point, but the main issue on the table as far as this PMA as far as I can see is, is it effective? Dr. Grimmitt, is sort of, basically in his slide presentation proposed that it's not. And looking at the data presented by the sponsor, I have difficulty convincing myself that I would recommend this to a patient.

We have a cohort that starts off with an average of 1.68 diopters. Twelve months later they are 0.49 diopters on average. And reading the numbers off the graphs, because I couldn't find them off the table, it looks like at 24 months they are on average around about 0.8. So it's only 50 percent effective two years out from the procedure. That's really where I think the rubber hits the road on this one.

DR. MC CULLEY: Other comments before we start to answer the FDA questions.

DR. HIGGINBOTHAM: Just to be fair, I think the numbers are small, as has been indicated several times. I would just qualify that last statement.

DR. BULLIMORE: Duly qualified.

DR. MANNIS: I don't know if it's been clarified by the sponsor as to why cycloplegia wasn't used as the baseline in this study pre-operatively?

DR. MACSAI: According to their protocols, it was performed pre-operatively at 6, 12, 18, and 24 months. So it's in the volume one or two.

DR. MC CULLEY: That was asked for before -- sponsors now have had time. When they come back, hopefully they can include that in the closing remarks.

DR. PULIDO: And point of clarification, I agree

with Dr. Higginbotham, the cycloplegic refractive spherical equivalents has been given to us in the white volume.

DR. MACSAI: I wanted the cycloplegic refractions comparing pre- to post- over time by low and moderate hyperopes, demonstrating refractive stability, out to 24 months, because that should tell us if it's stable.

DR. FERRIS: Just a general comment. I'd a big advocate of doing visual acuity examinations, as most of you know. But I also think you have to remember that there is a large subjective component to a visual acuity exam. It becomes important here, because there is no control group. It is somewhat surprising to me that there is only a tenth of a diopter difference between the cycloplege and the uncycloplege refractions. It may turn out to be that that's just the way it is. These people don't accommodate, even though they could see better if they did accommodate.

I assume the visual acuities are done one eye at a time. In theory at least, they could accommodate and see better. So I think it's important to also have the cycloplegic refractive data or some other hard endpoints to try to get a better assessment or more objective assessment.

In many ways, the subject of assessment is the most important thing in these patients. They have a disability.

They want to get better, and they either are or

they aren't. But it would be nice to have some other data as well. I think we have to remember that there is a big, subjective component. I don't know whether there is a placebo effect to this treatment, but I wouldn't be surprised if there is.

DR. MC CULLEY: Other questions, comments at this point before we start the questions from the FDA?

DR. WANG: I'd like to just make two very brief comments for the panel. One is in addition to what Dr. Grimmatt mentioned, the suitability from the statistical analysis of excluding the first 50, also, I cannot understand from the physics standpoint if you have the first 50, let's say overhydrated, and you just have a 0.5 diopter undercorrection for that group, why wouldn't that group result in the drop of stability long term?

Because all you're going to do is just parallelly, treating less 0.5 diopter. While on figure 2 in book 5, there is quite a difference, as Dr. Stulting pointed out that if you include the 50, it is not stable. If you exclude 50, it is stable at 18 to 24 months on this scale of the graph. So I have a conceptual problem of why a constant shift in the amount of correction would affect stability over time.

My last comment is I would like to know what is

the reason for against-the-rule astigmatism as the predominant post-op astigmatism, knowing that the treatment is symmetric? The reason I ask that is again, our focus is stability of treatment. Could it be such a specific type of astigmatism, which you know for example corneal disease endpoint occurs? But could that suggest in terms of having a predominant astigmatism post-op, any suggestion or cornea weakness or threatening instability? I'm just puzzled why symmetric treatment will give you asymmetry post-op.

DR. MC CULLEY: Thank you for your comments. Any other questions or comments now before we start to answer the FDA's questions?

DR. FERRIS: A quick comment. I think you have to be awfully careful looking at that flat part of cohort minus 50 at 18 and 24 months, because if you put some confident intervals around those points, maybe there is drift, maybe there's not drift. I just think we don't know yet.

DR. MC CULLEY: Because the numbers are so small?

DR. FERRIS: Yes.

DR. MC CULLEY: Malvina, would you like to put your questions up, please? I'll let you read them.

DR. EYDELMAN: Question 1, which cohort (original, updated or updated minus 50) do you believe to be the most appropriate for assessment of safety and efficacy of this

device?

DR. GRIMMETT: I think ideally I'd like to see updated minus 46. And I would like to see statistical analysis comparing the new updated numbers in a similar fashion to volume one, appendix G. Rerun with numbers with 46.

DR. MC CULLEY: Dr. Macsai, would you like to add to that?

DR. MACSAI: I'd like to see the same analysis, but I guess I need to see the analysis before I say which one I think we should use.

DR. VAN METER: This question is a little unfair, because we have longer follow-up for the original 46. We have the current technique that supposedly works better with the updated minus 50, but we don't have the time for those. So what we would like to do is have the time for the original 46, and the technique for the updated minus 50, and we don't have either one.

DR. EYDELMAN: This question was based on trying to make an assessment today with the data that is currently available.

DR. MC CULLEY: Would you like to respond to that?

DR. VAN METER: Well, I don't think either one of them are appropriate for assessment of safety and efficacy.

DR. MC CULLEY: Any other comments? Dr. Grimmett?

DR. GRIMMETT: Without seeing the statistical analysis of the 46 versus the rest, the poolability analysis, I believe we're left with looking at the updated cohort if we are going to make the decision today.

DR. FERRIS: I'd like to add to that it seems to me that if what we would come out with is a recommendation for a procedure, and those first 46 are a different procedure that the sponsor themselves said is not the procedure we want to use, I don't see how we can have those 46 or 50 useful. I still am looking forward to finding out the difference.

DR. MC CULLEY: So you would say updated minus 50?

DR. FERRIS: Yes, the other just seems useless.

DR. MC CULLEY: So updated minus 50 would be -- to answer your question the way you ask it, updated minus 50. Is that correct?

DR. FERRIS: Or 46.

DR. MC CULLEY: Well, we don't have minus 46, do we?

DR. FERRIS: Oh, well, I take that point.

DR. EYDELMAN: Question 2, has adequate refractive stability been demonstrated with this device by 6 months?

DR. MACSAI: No.

DR. MC CULLEY: Would you like to elaborate on that? That's enough?

DR. MACSAI: I just gave a presentation on it.

DR. MC CULLEY: Dr. Grimmatt. I don't want you to give it again.

DR. GRIMMETT: As indicated in my slide presentation, the answer is no from my standpoint.

DR. MC CULLEY: Does anyone else have any comment they would like to add?

DR. BULLIMORE: No.

DR. MC CULLEY: That didn't add.

DR. BULLIMORE: Definitely no.

DR. MC CULLEY: That's better. All right, 2b?

DR. EYDELMAN: Based on the refractive stability presented in this PMA, is the current follow-up of eyes treated sufficient to provide reasonable assurance of safety and effectiveness of this device?

DR. MC CULLEY: Dr. Grimmatt?

DR. GRIMMETT: I would recommend additional follow-up to the 24 month interval, as previously indicated. So my answer is no, primarily with regard to effectiveness.

DR. MC CULLEY: Is there agreement on that? Dr. Macsai?

DR. MACSAI: I would agree with Dr. Grimmatt and

recommend 90 percent accountability at the 24 month mark.

DR. MC CULLEY: Is there agreement on that?

DR. BULLIMORE: I could go with a little less than 90 percent. At 24 months I think 80 percent is a little more reasonable.

DR. MC CULLEY: Shoot for 90, accept 80?

DR. FERRIS: Why do we accept 80 percent? It is not an impossible task to get 90 percent follow-up. It seems to me that at the very least you ought shoot for 90 percent. I don't know whether there might be some circumstances where I would take 80, but I'm unhappy if we have 95 percent.

DR. MC CULLEY: I think that what we would say, we would want to shoot for 100 percent. Then the closer to it, the happier we have. We have in previous other guidance documents that have some parallels, set that mark at 90 percent.

DR. YAROSS: I would just like to point out the 90 percent standard I think was initially put in place with the idea that 10 percent loss to follow-up in one year was reasonable. So I think if you are talking about two years, it may be more appropriate to allow 10 percent per year as a realistic, real world situation.

DR. MC CULLEY: Yes, we make based adjustments

based on reality. As it relates to requested numbers and the guidance, I think we can still be flexible as time goes on.

DR. MACSAI: I agree, Dr. McCulley. I also think this is a new laser, and therefore the more data we can get to establish safety and efficacy, the better.

DR. MC CULLEY: No, question. I think that would affect our flexibility.

DR. WANG: I just wanted to make a comment. I second your opinions. I think in fairness to the sponsors that in a continuing improvement of hyperopic treatment given the low range of correction, I think that the cornea are willing to speak, to become steepened. Probably we should strive in addition to looking at this particular PMA, devise these documents so they have something to shoot for in terms of continuing proof, in terms of different parameters in the guidance document for hyperopic treatment.

DR. MC CULLEY: Dr. Rosenthal, you're sitting there close. Can you restate that?

DR. WANG: I think in fairness to the sponsor and trying to improve devices for hyperopic treatment strategy, given the uniqueness of hyperopic treatment, low range of correction, and the difficulty in steepening the cornea, perhaps at some point we should spend some time seriously in

coming down with some real numbers.

DR. MC CULLEY: A hyperopic guidance document in the future. I understand. Good suggestion.

DR. ROSENTHAL: That would really require probably another panel meeting. I think to be fair to the agency, we asked you all to do that back there, not about this device, but about the Excimer, and there was no consensus. But I appreciate the suggestion.

DR. MC CULLEY: The sentiment is that we need, in fairness to everyone, a guidance document for hyperopia that we do not have. That's a very good point, and it would be nice to have.

I think we have answered that question. Do you want further clarification?

DR. EYDELMAN: Yes, please. For the purposes of the record, I want a clarification as to whether you are referring to 80 percent accountability, or 80 percent of the eyes entered into the study seen at 24 months? Because when we calculate accountability, we take into account eyes not yet reaching that time period, and therefore you can have theoretically an 80 percent accountability with 50 or 60 eyes.

DR. MC CULLEY: I guess it would depend on the number to a degree that a certain number needs to reach the

24 months.

DR. EYDELMAN: That's the clarification I'm trying to obtain.

DR. MC CULLEY: And you're asking what that minimum number reaching 24 months would be with 90 percent accountability? Stay with number that we have used. We can adjust.

DR. ROSENTHAL: I don't think it's fair for us to change our definition of accountability. Everyone is now used to using it. Those that don't reach that time period are subtracted from the denominator. I think what Malvina is asking, is there a specific number? We know if there are 12 eyes out of 300, it's not adequate. Do you have a sense of the number of eyes that reach 12 months?

DR. MC CULLEY: It's 24 months. What is you are asking is how big or small a denominator would we accept.

DR. MATOBA: I think if you previously agreed that you would allow 2 percent loss per year, then at the end of 12 months it should be -- no, that's not true?

DR. MC CULLEY: No. We wanted 90 percent accountability.

DR. MATOBA: No matter how long the study goes.

DR. MC CULLEY: I don't think we qualified it.

DR. FERRIS: Did we have a minimum sample size in

the other guidance, which I thought was 300?

DR. MC CULLEY: I think so.

DR. FERRIS: So I didn't see any reason that you would hold hyperopia to a higher standard than myopia. So there have to be at least 300 that reach the 2 year visit, if people are happy with 2 years.

DR. MACSAI: Well, it's either 90 percent of the PMA cohort enrolled in Phase III clinical trials, or it's a number that provides you with an acceptable confidence interval, be it 300 or 400 or whatever, or 200. We have done it before, and I know that the FDA has provided us with this information to extract that number.

DR. EYDELMAN: I now understand the sense of the panel. We can move on. Question 3, the predictability of manifest refraction and the uncorrected visual acuity results decrease between 6 and 18 months. Does this raise concerns about treatment efficacy.

DR. MC CULLEY: I think we have answered that, did we not?

DR. ROSENTHAL: Could you answer it again?

DR. MC CULLEY: It does. That was the sentiment of the panel, I believe. For the record, yes.

DR. EYDELMAN: At six months post-treatment, 18 percent of all eyes examined had greater or equal to 1

diopter increase in cylinder. Most induced cylinder axes were in against-in-rule and oblique directions. Does this raise any concerns?

DR. GRIMMETT: Yes, I believe it raises a concern. The follow-up data did demonstrate a decrease in the astigmatism of direction that we all like it to go. I think for that issue, if the astigmatism is shifting, perhaps because of decreases, perhaps that could be reflected in the labeling. But it is a concern for these low level hyperopes that are having 1 diopter of astigmatism induction.

DR. VAN METER: The improvement in astigmatism probably reflects the same stabilizing force on the cornea, i.e., as Dr. Wang said, the cornea doesn't want to be steepened. If you look at the initial change, certainly there is some refractive instability, as Dr. Grimmatt showed. Part of that refractive instability is manifest with an increase in cylinders.

As you lose the cylinder, you also lose some of the refractive effect I think as the cornea heals its wounds. So these sort of go hand-in-hand. But I think the concerns of refractive instability are manifest by both regression of effect, and decrease in the increased cylinder.

DR. MC CULLEY: If we get what the panel has

already asked for, which is 300 eyes at 24 months, then it may take care of itself.

Any other comments?

DR. WANG: I think my answer is yes. In particular, the treatment is circular. The fact we are going to use 65 percent against-the-rule, I'm just wondering if that is suggesting in any way a weakening of the cornea. Again, the context of examining refractive stability. So the answer is yes.

DR. MC CULLEY: Next question.

DR. EYDELMAN: Question 5, visual symptoms data reveal photophobia and double vision to be the symptoms with the greatest change from pre-operative levels. Do increases in these visual symptoms constitute a safety concern?

DR. MACSAI: Well, it seems the sponsor has tried to address this by questioning these patients with a phone questionnaire. But it's my understanding that this data wasn't submitted for FDA review, the tabulations. Were they, of the phone questionnaire, or weren't they?

DR. EYDELMAN: The summary of this was submitted.

DR. MACSAI: Sorry. Got it.

DR. EYDELMAN: What was not submitted was the information on the updated cohort. But the phone questionnaire, the original was submitted.

DR. MACSAI: The original, but not the updated.

DR. MC CULLEY: Again, if we're going the route that we're going, which is requesting more, it's a moot point; 5b.

DR. EYDELMAN: Is the analysis of the updated patient questionnaire necessary prior to making a recommendation regarding approvability of this device?

DR. MACSAI: Yes.

DR. GRIMMETT: It seems to redundant to me to the last question. Didn't we just agree that we would like the updated questionnaire information? So certainly we would like that information on the review.

DR. MC CULLEY: Next question.

DR. EYDELMAN: Do the safety and effectiveness outcomes stratified by diopter of pre-operative hyperopia +0.75 to +1.99 diopter and +2.00 to +2.50 diopter support approval for the full range of hyperopia of +0.75 to +2.50 diopters of spherical equivalent?

DR. MACSAI: Not yet.

DR. MC CULLEY: Dr. Grimmer, would you like to add to that?

DR. GRIMMETT: I agree. As soon as we have the updated data, we will be in a better position to reanalyze the safety and effectiveness data. I believe it should be

stratified in the updated data as well.

DR. MC CULLEY: Other comments? Number 7?

DR. EYDELMAN: What are your recommendations for labeling regarding potential regression, cylinder induction, and visual symptoms? Do you have any additional labeling recommendations?

DR. MC CULLEY: Dr. Pulido, would you like to respond to that question?

DR. PULIDO: I would say that right now this is a moot point.

DR. MC CULLEY: Do you have any other questions for us?

DR. EYDELMAN: No, thank you.

DR. MC CULLEY: Does the panel have any other issues to add at this point?

DR. HIGGINBOTHAM: I guess in addition to the additional follow-up, I would like to see some analysis of whether or not there might be gender influence here. You have that? Okay, thank you.

DR. JURKUS: I am also wondering if a more detailed analysis about near-front acuity would be available.

DR. MACSAI: I would like to expand on Dr. Higginbotham's request for gender analysis in that this is

the patient population at high risk for dry eyes and keratoconjunctivitis and that may have an influence on the efficacy of the laser. So if they could make an analysis of that as a barrier.

DR. PULIDO: I'd like to thank again the sponsor for supplying, one, good accountability, and number two a good data set from which we could see the strengths and weaknesses.

DR. FERRIS: I'd like to follow-up on something Dr. Wang said. That is although I know we are not going to rewrite the guidance document, I'm concerned if the data at two years is showing a decrease, whether at least with the other laser system we have asked about documenting stability, and so I worry that we may or may not find two years to be the endpoint.

At some point you need to go until you document stability, or at least it would seem to me that I would I might know about stability, because my patients would probably want to know more than a two year effect. Is it going to level off or is it not. If hasn't leveled off, I think there may be concern bringing it back here.

DR. MC CULLEY: So what one would say if we were writing the guidance document would be minimum of two years for a new device, assuming that stability is demonstrated at

two years?

DR. PULIDO: And stability being what?

DR. MC CULLEY: It would have to be redefined for this group, as has been pointed out. That would be to be determined in the guidance. We don't have that.

DR. PULIDO: Shouldn't we tell the sponsor what we would like for stability, since we were asking for long-term results now? We need to be able to help them in that regard. What will we be happy with?

DR. MC CULLEY: Dr. Grimmett or Dr. Bullimore, either one.

DR. BULLIMORE: Primarily, I would like to see a little more data. I mean it's very difficult to make decisions on stability with so little data at the 24 months.

I reiterate my impression that at two years the technique appears to be on the order of 50 percent effective. I base that both on the cross-sectional data that has been presented -- I'm sorry, the longitudinal data that has been presented, but also the pair-wise comparison, looking at the change in the elegant integration of that data that was done in various people's heads. I think that will remain my primary concern.

DR. WANG: I just want to make a comment. I would like to echo Dr. Pulido's comment to the sponsor in this

well conducted study. I think the gist of the problem is the sponsor looked at the myopic guidance document and it seems to fit. However, I think there is definitely the need if FDA examines further hyperopic treatment devices, a clear guidance document.

Agenda Item: Open Public Hearing Session

DR. MC CULLEY: Any other comments? At this point that will conclude the panel discussion. We now have a 30 minute potential open hearing session. We will recognize individuals in the audience who wish to come to the podium to make comments. Each individual will be limited to five minutes.

Is there anyone in the audience that would like to come forward and speak? Ms. Thornton has one mail in that it had been prior agreed would be read.

MS. THORNTON: Dr. Edward Yavitz(?), and ophthalmologist from Rockville, Illinois has requested that the following remarks be read into the record, since he was unable to present them himself. Dr. Yavitz is an investigator Laser Sight.

"The amount of hyperopia treated in this study should be broken down into 0.5 diopter increments by age of patient and sex. If the degree of pre-operative hyperopia is skewed for higher amounts in the oldest patients, and

lower amounts in the youngest patients with better immune systems, and is also lumped into only two groups by degree of hyperopia by age or sex, then regression could be mapped."

"It is necessary to provide the refraction results in cycloplegic terms and not manifest. Manifest refractions are meaningless especially on those having less than 1.25 diopters of pre-operative hyperopia. Once could have total regression while refracting such a patient, and still categorize it as stable success if using the term less than 1 diopter."

Thank you.

DR. MC CULLEY: See no other requests for individual to speak in the open public hearing, that session is now closed.

We now have five minutes allotted to the FDA for closing comments, and then the sponsor. You each will have five minutes. Does FDA have additional closing comments?

Agenda Item: FDA Closing Comments

DR. ROSENTHAL: No.

DR. MC CULLEY: Thank you. We now have the opportunity for the sponsor to have five minutes for closing comments.

Agenda Item: Sponsor Closing Comments

DR. KOCH: I just want to re-emphasize that we had good follow-up. We have over 90 at 18 months. In the low hyperopic group we have 20/40 or better that is consistent from 6 months to 18 months, and the 20/20 group is also consistent. So even though we need a lot of patients at 24 months, we had great acuities that maintained themselves.

If you look at the uncorrected acuities, you saw them for the groups as whole, the uncorrected acuities in these patients are 20/26, 20/24, and 20/25. And I think those are extraordinarily good data, and demonstrate good efficacy.

The moderate hyperopes are lower, and was pointed out, I think that's the 20/40 or better, 20/20 or better. But if you look at their mean uncorrected acuity, it is 20/30, 20/34, and 20/34. So these patients are still satisfied. They have confidence intervals that incorporate the FDA criteria, even though it is for myopia, and these are happy patients.

You have seen the regression curves. You have seen that with the original cohort they go to 26.3 months. With the new data we have shown that with the drier technique the stability endpoint is reached with no regression at 20.5 months. So we think that these data demonstrate in fact that it is adequate for approval.

Certainly, again I would challenge you that with regard to any safety data, I think we have already shown in the astigmatic data and the other data that this is not a safety issue, and that the efficacy data in fact at 18 months are outstanding.

DR. MC CULLEY: You still have three minutes. Are there any other comments? I see Dr. Stulting.

DR. STULTING: Over the years the FDA and the Ophthalmic Devices Panel have viewed a number of refractive surgical devices. It is common knowledge that approved refractive technologies in the United States are years behind those available outside this country. US ophthalmologists and patients must still leave this country in order to access technologies that we know to be better on the basis of public scientific data, common sense, and personal experience.

Indeed, the international users of this device are unable to understand why it would not receive FDA approval on the basis of the clinical data presented today. You have before you an application for a device that effectively treats low hyperopia with a low level of risk that is unique among refractive procedures.

Uncorrected and best corrected acuity is excellent and remains so through 18 months, as you just saw. There is

a small amount of post-operative refractive change, but the procedure is stable by the FDA's own definition at six months. Moreover, it shows a more favorable regression profile than any published refractive laser study.

It is important that the same standards be used to judge this PMA as have been used to judge similar applications that have recently come before you. This clearly does not appear to be occurring today. As your colleague and a potential user of this device, I strongly urge you to recommend approval of this PMA. We need to reverse the current trends so that new, safe, and effective technologies that are available outside of the United States are made available to patients and surgeons in this country in a timely manner.

DR. MC CULLEY: Does the sponsor have any other comments? The indication is no. Ms. Thornton will now read the voting options.

MS. THORNTON: Just to refresh your memory, the panel's recommendation options for the vote are as follows: approval, there are no conditions attached; approvable with conditions.

The panel may recommend that the PMA be found approval subject to specified conditions such as physician or patient education, labeling changes or further analysis

of existing data. Prior to voting, all the conditions are discussed by the panel, and listed by the panel chair.

Number three, not approvable. The panel may recommend that the PMA is not approvable if the data do not provide reasonable assurance that the device is safe, or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

DR. MC CULLEY: Dr. Grimmer, you have been collecting the data as we have been going along and scribing for us. Would you like to make a recommendation?

DR. GRIMMETT: The consensus I believe, and I will add some comments regarding additional data that people have asked for is that the current PMA in its current form is not approvable because reasonable assurance has not been given that the device is effective under the conditions prescribed, recommended, or suggested in the proposed labeling.

Issues regarding future submission will include cycloplegic data for all time intervals. Statistical analysis is requested specific to the first 46 cases. The data should be presented as the updated cohort minus 46. We would like the updated questionnaire regarding visual symptoms. And Drs. Higginbotham and Jurkus were talking

about requiring or asking for gender analysis, and I believe near-point acuity.

DR. MC CULLEY: That's the motion with added information. Is there a second to the motion?

DR. GRIMMETT: I didn't mention the number of patient required. Was the consensus 90 percent accountability, with minimum of 300? I wasn't clear.

DR. MC CULLEY: I believe so, at 24 months.

DR. GRIMMETT: We will add that as an amendment.

DR. MACSAI: Second.

DR. MC CULLEY: The motion has been made and seconded. Is there further discussion of the motion on the floor? Seeing none, all in favor of the motion signify by raising your hand high. It's unanimous.

[Whereupon, the motion was unanimously approved.]

DR. MC CULLEY: Dr. Grimmatt summarized, but we do need to have each panel member indicate why they voted as they did. We'll start at the other side over here.

DR. FERRIS: Well, as others mentioned, I commend the presenters, the sponsor for the data they have collected thus far. But for the reasons that were outlined by Dr. Grimmatt and Dr. Macsai, I think additional data is necessary before we have a good sense of both the safety and efficacy. It's apparent this does something, but a little

bit more data is needed.

DR. VAN METER: I voted not approvable. I believe the device is reasonably safe. I think the sponsors have shown that to my satisfaction. I have questions about the efficacy because the instability of the refraction and the regression.

The last table that was shown showed seemingly stability had percent of patients in the Y axis. And it would be more helpful to have the actual refraction data, ideally a cycloplegic refraction data, and show that to be stable, rather than have a percentage of patients that is 20/20.

DR. MACSAI: I voted not approvable. This is a new refractive laser. Despite the fact that the sponsor has done a great job in providing data in an organized, reviewable manner, it is just too soon to tell. The data reviewed to date demonstrates refractive drift and decreased efficacy over time. There is an increase in astigmatism with a progressive axis shift. Analysis of the total hyperopia as measured by cycloplegic refraction will determine the true efficacy of this procedure, and with further follow-up we will be able to better determine the safety and efficacy.

DR. JURKUS: I voted not approvable for the same

reasons that have been indicated.

DR. HIGGINBOTHAM: I voted not approvable considering I think the need for additional follow-up as evidenced by the increasing symptoms that patients are complaining about, as well as the lack of refractive stability long-term. I think we really do need to see what happens with these patients over time.

DR. PULIDO: I voted not approvable, again because I think not so much the safety data, but the effectiveness data. We need to have longer-term results to make sure we're not putting out to the American public, a new technique that is not stable over the long run.

DR. SUGAR: I voted not approvable. I believe the procedure is safe. I believe that the effectiveness is disappointing and further data will either confirm or refute that. I disagree with the 90 percent requirement. I don't think that that is realistic, but otherwise I agree with the vote.

DR. BULLIMORE: I voted not approvable. While I will accept that the device is reasonably safe, the efficacy data is somewhat disappointing. I believe that both sponsor and reviewers and indeed FDA have been hampered by the lack of a guidance document, but nonetheless one can apply some common sense to this data and look at the degree of change

that has been attempted, and place the actual achieved change at different time intervals in the context of what is being attempted. Based on that, I don't think that the sponsor has to date demonstrated efficacy.

DR. GRIMMETT: The average consumer will likely want more than a temporary refractive effect. Since there is a paucity of reliable, long-term data that cannot reasonably substantiate critical stability issues, I voted that the PMA is not approvable primarily due to effectiveness issues. I do believe the PMA shows that the procedure is reasonably safe.

DR. MATOBA: I voted that this procedure is not approvable for reasons elucidated by Dr. Grimmert and Dr. Macsai. I also agree with Dr. Sugar's comments regarding the accountability.

DR. MANNIS: I voted not approval primarily based on lack of demonstration of efficacy.

DR. WANG: I voted for not approvable. I do want to share the sentiment. As a refractive surgeon there is a need of the American public to have refractive surgical procedures offered to them in a timely manner, with good conscious consideration of all parameters. This study is well conducted. It does fit the myopic guidance document, however, it's not approvable based on our discussion. This

heightens further the need of FDA to come up with specific guidance document for the correction of hyperopia, since it is a different animal.

DR. MC CULLEY: Ms. Thornton, do you have closing remarks or a comment?

MS. THORNTON: I just wanted to in closing, first of all thank the panel for a lot of hard time reviewing, as well as deliberating today. I want to ask them please to take -- anything that is pertaining to this document should be put back behind the panel table, as you did with the first document this morning for pick up. Anything left on the table will be destroyed as well. So please take your notebooks with you or whatever out of the packs that you want to keep with you for tomorrow's deliberations.

Again, I want to thank you. It's been a long day, and we appreciate your hard work and attention to our needs.

DR. MC CULLEY: I would like to thank everyone for what has been I think a job well done. There were very professional presentations and panel discussions both this morning and this afternoon. With that, we will adjourn.

[Whereupon, the meeting was recessed at 6:10 p.m., to reconvene the following day, Friday, July 23, 1999, at 8:00 a.m.]