

UNITED STATES OF AMERICA  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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OPHTHALMIC DEVICES PANEL MEETING

102ND MEETING

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FRIDAY  
NOVEMBER 30, 2001

*This transcript has not been reviewed and FDA makes no representation regarding its accuracy.*

The panel met at 9:45 a.m. in the Whetstone Room of the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Joel Sugar, Interim Chair, presiding.

Present:

- JOEL SUGAR, M.D., Interim Chair
- ARTHUR BRADLEY, Ph.D., Voting Member
- MICHAEL R. GRIMMETT, M.D., Voting Member
- ALLEN C. HO, M.D., Consultant
- ANDREW J. HUANG, M.D., Consultant
- JANICE M. JURKUS, O.D., Consultant
- WILLIAM D. MATHERS, M.D., Consultant
- ALICE Y. MATOBA, M.D., Voting Member
- RONALD E. MCCARLEY, Industry Representative
- TIMOTHY T. McMAHON, O.D., Consultant
- JOSE S. PULIDO, M.D., Consultant
- JAYNE S. WEISS, M.D., Voting Member
- SARA M. THORNTON, Executive Secretary

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

(9:49 a.m.)

DR. SUGAR: I'd like to call this meeting of the Ophthalmic Devices Panel to order. And have introductory remarks from Sara Thornton.

MS. THORNTON: Is everybody here? All present and accounted for?

Good morning and welcome to the 102nd meeting of the Ophthalmic Devices Panel. Before we proceed with today's agenda, I've a few short announcements to make.

I would like to remind everyone, that's Panel, public, FDA, to sign in on the attendance sheets in the registration area just outside the meeting room.

All of the public handouts for today's meeting are available at the registration table.

If there are messages for Panel Members and FDA participants, information or special needs, they should be directed through Ms. Ann-Marie Williams, Ms. Shirley Meeks or Mr. Hashim Khalif, who are available in the registration area.

The phone number for calls to the meeting area here is 301/948-8900 and instruct your people if you contact them in advance for something that they

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1 need to just ask for the FDA registration desk.

2 In consideration for the Panel and the  
3 sponsor, the Agency, we ask that those of you with  
4 cell phones and pagers either turn them off or put  
5 them on vibrator mode while you are in this room.

6 We ask that all meeting participants  
7 please speak into the microphone and give your names  
8 clearly, so that the transcribers will have an  
9 accurate recording of your comments.

10 The next Ophthalmic Devices Panel meeting  
11 will be on Thursday and Friday, January 17th and 18th,  
12 2002. All available information for that meeting will  
13 be on the Advisory Committee website in approximately  
14 one week.

15 Now at this time I'd like to extend a  
16 special welcome and introduce to the public the Panel  
17 and the FDA staff, three Panel Consultants who are  
18 with us for the first time today and our new Industry  
19 Rep. One of our new consultants, beginning with Dr.  
20 Allen Ho comes to us from Philadelphia where he is an  
21 Associate Professor of Ophthalmology at the Thomas  
22 Jefferson University School of Medicine and an  
23 Associate Surgeon with the Retinal Service at the  
24 Wills Eye Hospital. Dr. Ho, we welcome you.

25 Dr. Andrew Huang is from Minneapolis,

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1 Minnesota where he is an Associate Professor and the  
2 Director of the Cornea and External Disease Service of  
3 the Department of Ophthalmology at the University of  
4 Minnesota. We welcome you also, Dr. Huang.

5 And our third new Panel Consultant, Dr.  
6 William Mathers is from Portland, Oregon where is  
7 Professor of Ophthalmology at the Oregon Health  
8 Sciences University, Casey Eye Institute and is a  
9 specialist in cornea and external disease. Welcome,  
10 Dr. Mathers.

11 And Mr. Ronald "Rick" McCarley, the  
12 Industry Representative to the Panel who is President,  
13 CEO and Founder of Ophtec USA, Inc. Welcome, Rick.

14 We very much appreciate your commitment to  
15 serve and we welcome you, all of us welcome you to the  
16 Panel table today.

17 To continue, will the remaining Panel  
18 Members please introduce themselves beginning with Dr.  
19 Pulido.

20 DR. PULIDO: Jose Pulido, Professor and  
21 Head of the Department of Ophthalmology, University of  
22 Illinois, Chicago.

23 DR. McMAHON: I'm Tim McMahon, Professor,  
24 University of Illinois, Chicago.

25 MS. THORNTON: I can't hear Dr. McMahon

1 very clearly. You want to check that one out.

2 DR. McMAHON: Tim McMahon, Professor,  
3 University of Illinois, Chicago.

4 DR. BRADLEY: Arthur Bradley, Professor of  
5 Vision Science, Indiana University.

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

9 DR. SUGAR: Joel Sugar, Professor of  
10 Ophthalmology, also University of Illinois, Chicago.

11 DR. GRIMMETT: Michael Grimmett, Assistant  
12 Professor, University of Miami, Bascom Palmer Eye  
13 Institute.

14 DR. MATOBA: Alice Matoba, Associate  
15 Professor, Department of Ophthalmology, Baylor College  
16 of Medicine.

17 DR. JURKUS: Jan Jurkus, Professor of  
18 Optometry, Illinois College of Optometry in Chicago,  
19 Illinois.

20 DR. ROSENTHAL: Ralph Rosenthal, Director,  
21 Division of Ophthalmic and ENT Devices.

22 MS. THORNTON: Thank you, Panel. I'd like  
23 to note for the record and with regret, that Ms.  
24 Glenda Such, our new Panel Consumer Representative  
25 cannot be with us today. Earlier this week she had to

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1 undergo surgery so we wish her a speedy recovery and  
2 we look forward to having with us at our January  
3 meeting.

4 DR. SUGAR: Thank you, Sally. We now have  
5 time for an open public hearing.

6 MS. THORNTON: Wait, I've got two more  
7 things.

8 DR. SUGAR: I missed something. We still  
9 have time for that.

10 MS. THORNTON: Two more things. Okay,  
11 here we go. I'd like to read the conflict of interest  
12 statement for this meeting. The following  
13 announcement addresses conflict of interest issues  
14 associated with this meeting and is made part of the  
15 record to preclude even the appearance of an  
16 impropriety. To determine if any conflict existed,  
17 the Agency reviewed the submitted agenda for this  
18 meeting and all financial interests reported by the  
19 Committee participants. The conflict of interest  
20 statutes prohibit special government employees from  
21 participating in matters that could affect their or  
22 their employer's financial interests. However, the  
23 agency has determined that participation of certain  
24 members and consultants, the need for whose services  
25 outweighs the potential conflict of interest involved

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1 is in the best interest of the government. Therefore,  
 2 a waiver has been granted for Dr. Michael Grimmett,  
 3 for his imputed interest in a firm at issue that could  
 4 potentially be affected by the Panel's  
 5 recommendations. The waiver allows this individual to  
 6 participate fully in today's deliberations. Copies of  
 7 this waiver may be obtained from the Agency's Freedom  
 8 of Information Office, Room 12A-15 of the Parklawn  
 9 Building.

10 We would also like to note for the record  
 11 that the Agency took into consideration certain  
 12 matters regarding Drs. Arthur Bradley, Timothy McMahon  
 13 and Allen Ho. These Panelists reported past and/or  
 14 current financial interests in firms at issue, but in  
 15 matters not related to today's agenda. The Agency has  
 16 determined, therefore, that they may participate fully  
 17 in today's deliberations.

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

24 With respect to all other participants, we  
 25 ask in the interest of fairness, that all persons

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1 making statements or presentations disclose any  
2 current or previous financial involvement with any  
3 firm whose products they may wish to comment upon.

4 I'd like to now read the appointment to  
5 temporary voting status. Pursuant to the authority  
6 granted under the Medical Devices Advisory Committee  
7 Charter dated October 27, 1990 and as amended, August  
8 18, 1999, I appoint the following individuals as  
9 voting members of the Ophthalmic Devices Panel for  
10 this meeting on November 30, 2001: Drs. Janice  
11 Jurkus, Allen Ho, Andrew Huang, Timothy McMahon,  
12 William Mathers, Jose Pulido, Joel Sugar. In  
13 addition, I appoint Dr. Joel Sugar to serve as Interim  
14 Panel Chair for the duration of this meeting.

15 For the record, these individuals are  
16 special government employees and consultants to this  
17 Panel or other Panels under the Medical Devices  
18 Advisory Committee. They have undergone the customary  
19 conflict of interest review and have reviewed the  
20 material to be considered at this meeting. This is  
21 signed David W. Feigal, Jr., M.D., M.P.H., Director of  
22 the Center for Devices and Radiological Health, dated  
23 November 16, 2001.

24 Thank you, Joel.

25 DR. SUGAR: Thank you again. We now have

1 time for open public hearing. If anyone has public  
2 statements to make, they need to identify themselves  
3 and state any financial conflicts or potential  
4 conflicts.

5 There is a submission by mail that Sally  
6 will read.

7 MS. THORNTON: This is a letter submitted  
8 to be read at this meeting by Dr. I. Howard Fine,  
9 President of the American Society of Cataract and  
10 Refractive Surgery, Clinical Associate Professor of  
11 Ophthalmology, Casey Eye Institute, Oregon Health and  
12 Sciences University.

13 "Dear FDA Panel Members, unfortunately, I  
14 was not able to attend today's Panel meeting scheduled  
15 to review the conductive keratoplasty procedure.  
16 However, in my absence, I would like to request that  
17 this letter be read aloud on my behalf. As part of  
18 full disclosure, I would like to inform the Panel that  
19 I am a member of Refractec's Medical Device Advisory  
20 Board. However, I hold this position gratis. I am  
21 not paid for my time to participate on the Board, nor  
22 do I have an equity position in the company. As a  
23 Medical Advisor, I feel that the outcomes from the  
24 clinical trial are as safe and effective as those  
25 presented by other refractive technologies. I make

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1 this statement with confidence as I am current  
2 President of the American Society of Cataract and  
3 Refractive Surgery and in this role have the  
4 opportunity to see and review many scientific  
5 presentations on refractive procedures. One very  
6 promising aspect of conductive keratoplasty is the  
7 potential for the technique to not induce dry eye  
8 post-operatively. As we all know, Lasik transects the  
9 cornea nerves, therefore inducing dry eyes in most  
10 patients. The investigators participating in the  
11 conductive keratoplasty trial have all reported little  
12 or no dry eyes post-operatively with this technology.  
13 I feel that the addition of another refractive  
14 technology will only strengthen our ability to  
15 practice medicine and allow us to provide our patients  
16 with the most appropriate procedure for them and their  
17 condition. For these reasons, I respectfully ask the  
18 Panel Members to approve conductive keratoplasty,  
19 allowing the Members of the ASCRS and ophthalmologists  
20 throughout the U.S. to utilize this technology.  
21 Sincerely, Dr. Howard Fine."

22 Thank you, Dr. Sugar.

23 DR. SUGAR: Thank you. This now closes  
24 the open public hearing session and we'll move on to  
25 the open committee session and we'll begin with a

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1 presentation by Dr. Statland from the FDA.

2 DR. STATLAND: Good morning. It's nice to  
3 be here for a number of reasons. One, it's always  
4 good to get out of the shop occasionally and see the  
5 real world events in front of us and this Panel  
6 Meeting is an example of a very important real world  
7 event. And second, in a very general way, to  
8 acknowledge all of you on the Panel who diligently  
9 look at the material given to you, make a scientific,  
10 clinical and pragmatic assessment of the information  
11 and give us your best recommendations.

12 I also for the third reason I'm here, is  
13 to give some plaques and some awards for individuals  
14 who served the FDA and there are four individuals that  
15 I'm going to acknowledge today and if you'll just bear  
16 with me. I have a short paragraph about each of you,  
17 so when I mention your name, don't be too concerned  
18 and I'll give you information.

19 First of all, one individual who actually  
20 received her placque earlier is Marcia, where is she?  
21 Marcia Yaross, Dr. Yaross is the Director of  
22 World-wide Regulatory Affairs and Medical Compliance  
23 for Allergen of Irvine, California. She graduated  
24 Reed College in Portland, Oregon with a degree in  
25 Biology and completed her doctorate in Cell and

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1           Developmental Biology at the University of California  
2           in Irvine. After a career in Biological Research, she  
3           entered the field of regulatory affairs as a  
4           Regulatory Affairs Coordinator for a major  
5           manufacturer of ophthalmic devices and has  
6           responsibility for many of the types of devices  
7           reviewed by the Ophthalmic Devices Advisory Panel.  
8           And as you know, she was the Industry Representative.  
9           Thank you for time and effort.

10                           Now for the three individuals here on the  
11           Panel, okay, the first is for Joel Sugar. Dr. Sugar,  
12           as you probably all know, is a Professor of  
13           Ophthalmology, the Director of Cornea Service and Vice  
14           Chair of the Department of Ophthalmology at the  
15           University of Illinois, Eye and Ear Infirmary in  
16           Chicago. He graduated from the University of Michigan  
17           Medical School and completed a residency in  
18           Ophthalmology at Washington University in St. Louis  
19           and a post-graduate fellowship in Cornea and External  
20           Disease at the University of Florida Medical School in  
21           Gainesville. Dr. Sugar is currently on the Board of  
22           Directors of the Eye Bank Association of America and  
23           also is on the Accreditation Committee and the Medical  
24           Advisory Board where he served as Chairman from 1991  
25           to 1996. He has published extensively and is

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1 internationally recognized for his research and  
2 publications on many specific aspects of corneal  
3 surgery, in addition to addressing numerous issues on  
4 corneal diseases, contact lens, intraocular lenses.  
5 Dr. Sugar and the two other individuals will be  
6 basically acting as special government employees at  
7 this particular meeting, so I will hand to him and to  
8 all the others both a letter from Linda Suydam,  
9 expressing in the same words of appreciation as well  
10 as this plaque for recognition of distinguished  
11 service.

12 DR. SUGAR: Thank you very much.

13 DR. STATLAND: My pleasure. The next  
14 individual to be recognized is Dr. Janice Jurkus who  
15 is a Professor of Optometry at the Illinois College of  
16 Optometry in Chicago. She received her Optometry  
17 degree from the Illinois College of Optometry and a  
18 Master's in Business Administration from Loyola  
19 University, also from Chicago. In addition to her  
20 professional involvement as a contact lens clinician,  
21 educator and coordinator of practice management, she  
22 is chairperson of the Faculty Council Executive  
23 Committee. Dr. Jurkus is a Fellow of the  
24 International Association of Contact Lenses Educators,  
25 a Fellow of the American Academy of Optometry and

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1 serves on the editorial board of Optometric  
2 Management. She has lectured and published  
3 extensively on contact lens materials and design,  
4 clinical complications, patient education and informed  
5 consent and is internationally recognized for her  
6 expertise.

7 DR. JURKUS: Thank you very much.

8 DR. STATLAND: My pleasure. The last  
9 individual to receive the award is Dr. Jose Pulido.  
10 Dr. Pulido is Professor and newly appointed  
11 Chairperson of the Department of Ophthalmology,  
12 University of Illinois Eye and Ear Infirmary in  
13 Chicago. He received his Bachelor's and Master's  
14 degrees from the University of Chicago in four years  
15 and consequently his M.D. from Tulane University  
16 School of Medicine in New Orleans. Following his  
17 Ophthalmology residency at the University of Illinois,  
18 he completed a fellowship in vitreoretinal surgery at  
19 the Bascom Palmer Eye Institute, University of Miami  
20 School of Medicine in Miami. He also has an M.B.A.  
21 from the University of Iowa. He is presently the  
22 National Director for Diabetes 2000 and serves as an  
23 editor for EyeNet. In addition, he's reviewer for  
24 numerous publications that include the Archives of  
25 Ophthalmology, American Journal of Ophthalmology, and

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1 Investigative Ophthalmology and Visual Sciences. Dr.  
2 Pulido is a Member of the Retina Society, the Macula  
3 Society, the American Uveitis Society and the American  
4 Ophthalmology Society. Congratulations.

5 DR. PULIDO: Thank you very much.

6 DR. STATLAND: As I listen to myself speak  
7 and realize all the attributes that all of you have  
8 and all the other Panelists as well, as I said before,  
9 I think we're so fortunate. We benefit so much from  
10 the excellent input that you give to us. We listen  
11 well, we are interested in what you have to say and  
12 just to state one more time that those individuals who  
13 have completed their term are acting today as special  
14 government employees and we appreciate that as well.  
15 So thank you for giving me this opportunity of being  
16 here and making these presentations. Have a great  
17 meeting.

18 (Applause.)

19 DR. SUGAR: Thank you very much. Dr.  
20 Statland.

21 DR. PULIDO: Mr. Chairman, I would like to  
22 say some words, this being my last meeting here and  
23 that is over the last few months, we've heard a lot  
24 about public safety and public safety officers and I  
25 can assure you that over these last four years I have

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1 had the opportunity to work with some wonderful public  
2 safety officers. These people in the FDA walk a very,  
3 very fine line between the needs of our private  
4 enterprises here in the United States and the need for  
5 public safety and I know that they are extremely  
6 pushed to try to do the best they can to serve both  
7 their constituencies and it's been an honor and a  
8 privilege to have worked with them. Thank you.

9 DR. SUGAR: I'd like to now move on to the  
10 Division Update. Dr. Rosenthal?

11 DR. ROSENTHAL: The only thing I have, Mr.  
12 Chairman, is that the -- which is not related to  
13 Ophthalmology, but is part of the Division, so I will  
14 update you, is that we've been fortunate enough to  
15 attract a new Branch Chief for our Ear, Nose and  
16 Throat Branch who is Eric Mann who is an  
17 otolaryngologist who comes to us from NIH and you will  
18 not have the opportunity and the pleasure to work with  
19 him, unless there's a combined device in which ENT and  
20 Eye is developed. I just wanted you to know that he  
21 has joined us and we are overwhelmingly delighted that  
22 he has agreed to accept the post.

23 DR. SUGAR: Thank you. Dr. Beers, Donna  
24 Lochner and Dr. Saviola, do you want to -- Donna is  
25 not here? Okay.

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1 DR. BEERS: I'm Everette Beers, Chief of  
2 the Diagnostic and Surgical Devices Branch. I just  
3 want to update you on some recent PMA approvals. We  
4 approved the VisX for Lasik mixed astigmatism, that  
5 was P930016, Supplement 14. And we approved the  
6 LaserSight for Lasik myopic astigmatism, P980008,  
7 Supplement 5. I won't go into all the indications on  
8 that, but those are approvals, supplemental approvals  
9 since our last meeting.

10 The Diagnostic and Surgical Devices Branch  
11 has been extraordinarily busy with clinical trials  
12 that I can't discuss here and with other issues that  
13 may not be of interest to you, but we are trying to  
14 work in everyone's best interest. Thank you.

15 DR. SUGAR: Thank you, Dr. Beers. Dr.  
16 Saviola?

17 DR. SAVIOLA: Good morning. As the former  
18 Acting Chief of the ENT Branch, as well as Branch  
19 Chief of the EDB I'm also delighted that Dr. Mann has  
20 joined us in the division.

21 I'd like to update the Panel on recent  
22 approvals of two 30-day extended wear contact lenses  
23 and give you a little bit of information about what  
24 we're doing with them. The Focus® NIGHT &  
25 DAY/otrafilcon contact lens was reviewed at the July

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1 Panel Meeting and it was approved October 11th. This  
2 soft contact lens is indicated for the correction of  
3 refracted ametropia and also a number of alternate  
4 designs such as toric and progressive designs were  
5 approved with the spherical design. The lens may be  
6 prescribed for daily or extended wear for up to 30  
7 nights of continuous wear, for removal -- with removal  
8 for disposal or cleaning as recommended by the eye  
9 care professional.

10 A precaution statement was included in the  
11 labeling that states at the extremes of the power  
12 range above +10.00 or -15.00 diopter oxygen  
13 transmissibility is slightly below the established  
14 threshold level required to prevent overnight corneal  
15 edema. We did not put a power restriction in the  
16 indication itself.

17 In the clinical study section results  
18 there are a few bullets about other important safety  
19 results of this study and I'll just read three of  
20 those that 14 of the FOCUS® 9-day subjects experienced  
21 infiltrates during the first month of extended wear  
22 compared to five of the control and that the FOCUS® 9-  
23 day subjects experienced more than one endpoint,  
24 excuse me, the FOCUS® 9-day subjects experienced more  
25 than one endpoint 70 percent during the first month of

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1 the trial. And for both groups if the subject  
2 experienced an infiltrate event in one eye, the risk  
3 of a second event in the same or fellow eye was six  
4 times more likely as compared to having a first event.

5 The Bausch & Lomb Purevision balafilcon A  
6 contact lens was approved on November 20th under a  
7 supplemental submission to the existing PMA. This  
8 lens is indicated for daily or extended wear from 1 to  
9 30 days between removals for cleaning and disinfection  
10 or disposal. We did put a power restriction on this  
11 one. It's approved from +8.00 D to -20.00D when  
12 prescribed for up to 30 days of extended wear and it  
13 already had approval for + or -20.00 for daily wear or  
14 extended wear up to 7 days. And again, a precaution  
15 statement is included in the labeling that addresses  
16 extremes of the power range above +3.00 and -5.00  
17 diopter. Also that the rate of infiltrative keratitis  
18 was found to be higher with higher lens powers.

19 Now although this PMA was a second of a  
20 kind, it was originally scheduled for discussion at  
21 the September 21st Panel Meeting to discuss the need  
22 for post-market study and to provide the Panel an  
23 opportunity to review clinical data from a  
24 contralateralized study. Two primary Panel Reviews  
25 have been completed in preparation for the meeting.

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1           Due to the tragic events of September  
2           11th, the September 21st meeting was canceled. During  
3           subsequent discussion, it was decided that the primary  
4           clinical issues in the PMA did substantially duplicate  
5           information previously reviewed by the Panel.  
6           Additional homework assignments from two Panel Members  
7           were obtained to corroborate the recommendation of the  
8           two primary reviewers in lieu of full Panel  
9           discussion.

10           All four Advisory Panel Reviews  
11           recommended approval of the supplement from 1 to 30  
12           days. Therefore, we did not refer to the full Panel  
13           for a meeting and discussion.

14           As to our plans to better communicate the  
15           risks to both patients and practitioners, we have  
16           placed a variety of restrictions on these two extended  
17           wear lenses. For advertising, the advertising  
18           restriction was put into the approval order. Similar  
19           to drug advertisements, print ads for the new extended  
20           lenses must include a company information to describe  
21           the indications, contraindications, warning and  
22           precautions.

23           The company, in conjunction with FDA,  
24           developed a consumer information leaflet in a question  
25           and answer format similar to information available for

1 some prescription drugs in order to address this  
2 restriction for consumer advertisements, rather than  
3 to print the whole technical information from the  
4 package insert.

5 For labeling, practitioners will receive  
6 additional information in professional labeling. The  
7 package insert will consider a clinical study result  
8 section that describes the study and provides  
9 information on demographics, primary safety and  
10 efficacy outcome measures and also provides a quick  
11 reference to better understand the details of the  
12 preapproval study.

13 A brief description of the study and  
14 outcomes of the study will also appear in the patient  
15 information booklet as well.

16 As far as post-approval clinical studies,  
17 as a condition of marketing approval, each  
18 manufacturer must conduct a post-market study to  
19 characterize the risk of microbial keratitis and  
20 subsequent loss of best corrective visual acuity in  
21 the general population. Both the Ciba and B & L  
22 studies will involve about 100 sentinel monitoring  
23 sites. These prospective active monitoring studies  
24 are designed to provide data on 4500 to 5000 patient  
25 years of subjects wearing their 1-month lenses during

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1 a 1-year period.

2 The protocols call for monitoring subjects  
3 every six months for the one year, without the  
4 detailed evaluation of all the parameters usually  
5 measured in pre-approval study.

6 While the scope of these post-approval  
7 studies does fall short of the 20,000 subjects it  
8 would take to do a statistically rigorous clinical  
9 study, they will still provide an early indication for  
10 risks in the real world setting and help to answer the  
11 questions of long-term safety in the general  
12 population.

13 These labeling initiatives provide a  
14 better opportunity for practitioners and patients to  
15 make a wearing schedule decision based on an  
16 individual patient's response to lens wear and their  
17 acceptable level of risk.

18 Thank you very much.

19 DR. SUGAR: Thank you. If there's no  
20 other information to be updated from the Agency, I'd  
21 like to move ahead to discussion and review of PMA  
22 P010018. We'll begin with the sponsor presentation.  
23 The sponsor has one hour. I'd like each presenter to  
24 identify themselves at the beginning of their  
25 presentation.

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1 DR. GORDON: Good morning. My name is Dr.  
2 Judy Gordon. I have the pleasure of representing  
3 Refractec today as a regulatory consultant. Together  
4 with Dr. Jon Hayashida, Refractec's Vice President of  
5 Clinical Affairs, we will present to this Panel the  
6 clinical trial results submitted to the FDA in P010018  
7 for the ViewPoint Conductive Keratoplasty system. We  
8 will be joined by two of the clinical investigators  
9 who participated in the CK trial, Dr. Marguerite  
10 McDonald who has also served as Medical Monitor for  
11 the study, and Dr. Peter Hersh, who is an  
12 investigator.

13 Dr. Dan Durrie, another of the CK study  
14 investigators, has also joined us today add his  
15 clinical perspective as a refractive surgeon is  
16 involved in multiple clinical trials of new refractive  
17 surgery procedures. We appreciate the opportunity to  
18 present to this Panel and hope that our presentation  
19 elucidates the clinical data presented in this PMA.

20 Dr. Hayashida will begin the presentations  
21 with a brief discussion of the indication and the  
22 technology.

23 DR. HAYASHIDA: Thank you, Judy. Good  
24 morning. I am Dr. Jon Hayashida. I would like to  
25 share with you today some background information on

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1 the correction of hyperopia and the conductive  
2 keratoplasty procedure. Historically, the surgical  
3 correction of hyperopia has been considerably more  
4 challenging than myopic corrections in that it  
5 requires steepening of the central cornea. Currently,  
6 this is accomplished by means of excimer laser  
7 ablation and collagen shrinkage procedures that apply  
8 treatment to the peripheral cornea.

9 Thermal keratoplasty alters the cornea  
10 curvature by heating the stromal tissue in the  
11 periphery, causing collagen to shrink. Achieving an  
12 optimal collagen shrinkage thermal profile is  
13 critical. If the temperature profile is too low,  
14 minimal collagen shrinkage results. If the  
15 temperature profiles are too high, excessive tissue  
16 damage and eventual remodeling and regression of the  
17 effect occur.

18 The heating of corneal tissue can be  
19 accomplished by utilizing either laser light energy or  
20 radio-frequency energy.

21 As shown in this photograph, the viewpoint  
22 conductive keratoplasty system consists of a portable  
23 console that generates the radio-frequency energy, a  
24 lid speculum and a handpiece in which a small tip  
25 called the keratoplast tip is held. The keratoplast

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1 tip is used to deliver the energy for treatment, while  
2 the lid speculum serves as the return.

3 Conductive keratoplasty, or CD, involves  
4 the controlled interstromal delivery of  
5 radio-frequency energy to a depth of approximately 500  
6 microns in the corneal periphery. RF energy passes  
7 from a generator to a probe tip which is 450 microns  
8 in length by 90 microns in diameter into the corneal  
9 stroma and returns via the lid speculum.

10 The impedance of the corneal tissue  
11 results in a thermal effect that is controlled to  
12 achieve the optimal thermal profile for collagen  
13 shrinkage temperature along the entire length of the  
14 probe. This provides a homogenous and uniform  
15 cylinder of optimally constricted collagen to a depth  
16 of approximately 80 percent of the peripheral corneal  
17 thickness.

18 To demonstrate the column of constricted  
19 collagen, histology was performed on pig corneas. The  
20 image shown here is a transmission polarization  
21 micrograph of a CK treatment spot in a pig cornea  
22 which a corneal thickness of about 650 microns as 7  
23 days post-operative. The CK footprint has also been  
24 measured post-operatively in humans, using ultrasound  
25 biomicroscopy. On average, the CK cylindrical

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1 footprint measured 405 microns wide by 509 microns  
2 deep. We believe that it is the uniformity and depth  
3 of this footprint which contributes to the  
4 effectiveness of the CK procedure.

5 To achieve the optimal configuration for  
6 safe and long-lasting collagen shrinkage the CK  
7 treatment applications are of consistent power with an  
8 increase in the number of rings of applications to  
9 achieve greater levels of corneal steepening. The  
10 procedure spares the visual axis, offering an  
11 important potential safety feature.

12 As shown in this videoclip of a CK  
13 procedure, the optical zone marks of 6, 7 and  
14 millimeters act as a template for the treatment  
15 application. Once the optical zone marks are applied,  
16 the surgeon begins applying treatment spots superially  
17 and continues in a cross cornea fashion for each ring,  
18 moving from the most internal ring at the 6 millimeter  
19 zone to the outside ring at the 8 millimeter zone  
20 until all of the rings of treatment are complete.

21 The stop or cuff on the keratoplast tip  
22 aids in ensuring that the tip is inserted into the  
23 cornea perpendicular to the corneal surface for each  
24 spot.

25 Stria then begin to form between the

1 treatment spots creating a circumferential band of  
2 tightening. It is this tightening of the tissue which  
3 results in the steepening of the central cornea.

4 In fact, with confocal microscopy, we have  
5 been able to establish the continued presence of stria  
6 between treatment spots at 12 months post-operatively.  
7 These observations are consistent with the clinical  
8 effects observed post-CK.

9 In conclusion, we believe that the  
10 application of radio-frequency energy in the  
11 conductive keratoplasty procedure has clinical  
12 advantages over other methods of collagen shrinkage  
13 based on the mechanism of action. In support of this,  
14 Dr. Marguerite McDonald will present the safety and  
15 effectiveness data generated in the IDE clinical trial  
16 of conductive keratoplasty.

17 DR. McDONALD: Thank you, Jon. Good  
18 morning. I am Dr. Marguerite McDonald and I served as  
19 both the Medical Monitor and as principal investigator  
20 for the IDE clinical trial of conductive keratoplasty.  
21 I wish to share with you the clinical results of this  
22 phase 3 clinical trial designed to evaluate the safety  
23 and effectiveness of the Viewpoint CK system for the  
24 correction of hyperopia.

25 This is a list of the principal

1 investigators who participated in the CK trial. This  
2 group represents many leaders in corneal refractive  
3 surgery and also represents a mix of private  
4 practitioners and academic centers so several types of  
5 surgeons contributed to the CK clinical trial and to  
6 the understanding of this procedure. The CK clinical  
7 trial was designed and conducted in accordance with  
8 FDA guidance for hyperopia treatment. Eligible eyes  
9 within +0.75 to +3.25 diopters spherical hyperopia and  
10 had no more than -0.75 diopters refractive cylinder,  
11 translating into baseline cycloplegic spherical  
12 equivalent of +0.75 to +3.00 diopters. All treatments  
13 were based on pre-op cycloplegic refraction spherical  
14 equivalent with a treatment goal of full correction of  
15 spherical hyperopia. No cylinder corrections and no  
16 retreatments were performed in this study.

17 The standard effectiveness measures were  
18 improvement in uncorrected acuity, predictability of  
19 the refractive outcome, refractive stability, and  
20 patient satisfaction.

21 Safety parameters included measurement of  
22 best corrected vision, induced cylinder, endothelial  
23 cell loss, patient symptoms and as far as any clinical  
24 trial complications and adverse events.

25 A total of 401 eyes of 233 subjects were

1 enrolled in this study and demographics for this  
2 population are shown here. Consistent with other  
3 clinical trials of refractive surgery procedures, a  
4 larger number of women than men were enrolled and the  
5 mean age of the study population was approximately 55  
6 years.

7 Critical to any hyperopia study is the  
8 exclusion of latent hyperopes, therefore entry  
9 criteria for the study required that no more than  $>.05$   
10 diopter difference between the pre-op MRSE and CRSE  
11 would be allowed as demonstrated in this slide.  
12 Please note that in the original study protocol, 54  
13 eyes with CRSE of 1.00 to 4.000 diopters were  
14 enrolled. Additionally, you will note that two  
15 ineligible eyes were enrolled, accounting for the MRSE  
16 range extending to  $-0.38$  diopters.

17 Approximately half of all eyes enrolled  
18 had baseline MRSE and CRSE between 1.00 and 1.99 D and  
19 over a third of eyes had baseline MRSE of greater than  
20 or equal to 2 D. As I mentioned on the previous  
21 slide, eyes with up to 4.00 diopters of spherical  
22 equivalent were enrolled in the initial phase of study  
23 prior to a nomogram adjustment that limited the upper  
24 range of treatment.

25 This nomogram adjustment was based on the

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1 results of the 54 eyes treated in the initial phase of  
2 the CK clinical trial. Analysis of the outcomes of  
3 these eyes revealed overcorrection at the low end of  
4 the treatment range and under correction at the upper  
5 end of the range. On the basis of these data,  
6 Refractec implemented a reduction in the maximum  
7 treatment from 4.00 to 3.25 diopters of spherical  
8 hyperopia and the addition of an 8 spot treatment  
9 pattern for eyes with base.line CSRE of 0.75 to 0.85  
10 D.

11 Accountability in the study was excellent  
12 with at least 97 percent available eyes examined at  
13 each visit. Ninety-four percent of all eyes enrolled  
14 were available for analysis through the 9-month  
15 examination and just over 50 percent of eyes had  
16 reached the 12-month examination at the time the data  
17 base for this PMA was locked. As the medical monitor  
18 for this study, I've been very impressed with the  
19 effort to ensure that patients' follow-up is complete.

20 This flow chart shows the total population  
21 of 401 eyes enrolled and the relevant cohorts.  
22 Thirty-eight eyes were not treated with the current  
23 nomagram and are therefore not included in the  
24 effectiveness cohort of 363 eyes. The safety cohort  
25 includes all enrolled eyes with the exception of a

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1 single that was discontinued from the study prior to  
2 treatment.

3 Effectiveness data will be reported for  
4 the 363 eyes treated with the current nomagram while  
5 safety instability will be presented for all 400  
6 treated eyes.

7 We will now move on to a review of the  
8 effectiveness data generated in the CK clinical trial.  
9 Before describing the effectiveness outcomes in  
10 detail, I would like to review this summary of  
11 effectiveness. As you can see from this slide, key  
12 effectiveness targets established in FDA guidance were  
13 met. Uncorrected visual acuity of 20/40 or better  
14 exceeded the FDA target of 85 percent from the 6-month  
15 visit forward as did the proportion of eyes with MRSE  
16 within .50 diopter and within 1.00 diopter of plano.  
17 Targets were exceeded for change in MRSE less than or  
18 equal to a .50 diopter and less than or equal to 1.00  
19 diopter. Mean change per month was small, 0.03  
20 diopters between 6 and 9 months and increased  
21 nonsignificantly to 0.04 diopters per month between 9  
22 and 12 months.

23 We will now expand on the effectiveness  
24 parameters which included improvement in uncorrected  
25 visual acuity, predictability and stability of the

1 refractive outcome and patient satisfaction.

2 As shown in this slide, uncorrected visual  
3 acuity improved over the course of follow-up with the  
4 FDA target of 85 percent of eyes with 20/40 or better  
5 achieved at the 3-month examination. While the  
6 proportion of eyes with uncorrected acuity of 20/20 or  
7 better was low at the 1-month examination, this is  
8 likely a result of the slight overcorrection in  
9 refraction observed at 1 month. Additionally, it  
10 should be noted that these data reflect the outcomes  
11 of a single procedure since no retreatments or  
12 enhancements were performed in this study.

13 As shown in this graphical representation,  
14 uncorrected acuity improved from 1 in 3 months to the  
15 later examinations and excellent levels of uncorrected  
16 acuity were achieved at 9 and 12 months post operative  
17 with the FDA target of 85 percent 20/40 or better  
18 achieved from 3 months forward.

19 The FDA targets for predictability of the  
20 refractive outcome are defined as MRSE within a .50  
21 diopter of plano for 50 percent of eyes and within  
22 1.00 diopter for 75 percent of eyes.

23 Accuracy of the CK procedure exceeded the  
24 FDA targets at all study visits from 3 months. At 12  
25 months, close to 60 percent of eyes were within a .50

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1 diopter of plano and 91 percent were within 1 diopter.  
2 This level of accuracy of the refractive outcome is  
3 very good, particularly when considering that these  
4 results reflect the outcome of only a single procedure  
5 with no retreatments.

6 As shown in this graphical representation  
7 of predictability, the FDA targets for proportion of  
8 eyes within a .50 diopter of plano and within 1.00  
9 diopter of plano were met and exceeded by the 3-month  
10 visit with 56 percent of eyes with .50 diopter of  
11 plano and 83 percent within 1.00 diopter. These  
12 values increased at 6 months to approximately 60  
13 percent within a .50 diopter of plano and close to 90  
14 percent within 1.00 diopter of plano for the remaining  
15 visits through one year.

16 When examining a consistent cohort of 158  
17 eyes with all visits through 12 months, the  
18 predictability of the CK procedure is further  
19 established with approximately 60 percent of eyes  
20 within a .50 diopter of the target refraction and 90  
21 percent of eyes within 1.00 diopter of target.

22 Predictability of the CK procedure is  
23 presented here graphically to display the proportion  
24 of eyes that were under-corrected and over-corrected.  
25 This shows clearly that the proportion of eyes

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1 initially over-corrected decreased substantially after  
2 one month and under-correction was limited to a small  
3 number of eyes throughout the course of the study.

4           Refractive stability is another key  
5 effectiveness parameter and the FDA has identified  
6 four criteria for achieving stability. These include  
7 the proportion of eyes with a change of less than or  
8 equal to MRSE of .50 diopter and less than or equal to  
9 MRSE of 1.00 diopter. Mean change in MRSE of less  
10 than or equal to .50 diopter on an annualized basis  
11 and decreasing to an asymptote of 0, and inclusion of  
12 0 in the 95 percent confidence interval for mean  
13 change in periods preceding and after stability is  
14 established.

15           The stability target of 95 percent of eyes  
16 with a change of less than or equal to 1.00 diopter in  
17 MRSE between two refractions performed at least 3  
18 months apart identified in FDA guidance was achieved  
19 at both the 6 to 9 and 9 to 12 month intervals.  
20 Additionally, a paired analysis of mean change per  
21 month in MRSE shows very small changes in this  
22 parameter over time. Between months 6 and 9, the mean  
23 change per month in the manifest refraction was 0.03  
24 diopters while mean change was 0.04 diopters between  
25 9 and 12 months. However, these data did not achieve

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1 the remaining two FDA criteria for stability,  
2 including successive decreases in mean change over  
3 time and the confidence interval encompassing zero.

4 Stability of the cycloplegic refraction is  
5 shown in this slide. It is noteworthy that both the  
6 proportion of eyes within the stability parameters and  
7 mean change in MSRE over time are consistent with the  
8 same measures just shown for manifest refraction. The  
9 close match between the manifest and the cycloplegic  
10 refractive stability suggests that eyes with latent  
11 hyperopia were effectively screened out of the study,  
12 preventing masking of poor visual and refractive  
13 outcomes by accommodation.

14 Consistent with the analysis of stability  
15 of MSRE, mean change in CSRE by paired analysis was  
16 very small between 6 and 9 and between 9 and 12  
17 months. The upper limits of the confidence intervals  
18 were the same for both 3-month intervals and the  
19 standard deviation of the mean decreased over time.

20 When plotting both mean MSRE and mean CSRE  
21 over time, the close match between the manifest and  
22 cycloplegic refractions is again observed. As with  
23 all corneal steepening procedures there is an initial  
24 overcorrection, but this is relatively small following  
25 the CK procedure. This overcorrection has generally

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1        been acceptable to study patients. Emmetropia is  
2        reached at approximately 6 months and there is less  
3        than a .25 diopter of change between 6 and 12 months.

4                To more fully characterize the stability  
5        of the refractive outcome following CK, we have also  
6        examined how much of the intended correction is  
7        retained over time and, as you will see, approximately  
8        90 percent of the intended correction remains at 12  
9        months.

10                As for any elective surgery, patient  
11        satisfaction is a very important measurement of the  
12        procedure's effectiveness. Overall satisfaction is  
13        summarized in this slide. A large majority of  
14        patients were very satisfied or satisfied with the  
15        outcome of CK treatment. Approximately 9 to 12  
16        percent of patients were dissatisfied or very  
17        dissatisfied at 9 and 12 months. It should be pointed  
18        out that these findings are consistent with reports  
19        from other studies of refractive correction of  
20        hyperopia.

21                This summary slide once again demonstrates  
22        the strong effectiveness outcomes following CK with  
23        study outcomes meeting targets identified in FDA  
24        guidance for uncorrected acuity and predictability of  
25        refractive outcome.

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1           As we move to a discussion of safety  
2 parameters, please note that safety is reported for  
3 400 treated eyes. Key safety outcomes are summarized  
4 on this slide. As shown here, following the CK  
5 procedure, all FDA limits for safety were met in the  
6 study population. Only 1 percent of eyes lost more  
7 than two lines of BSCVA and best corrected acuity was  
8 20/40 or better in all eyes at 6, 9 or 12 months  
9 post-operative. Finally, the incidents of greater  
10 than 2D increase in induced cylinder was well below  
11 the current FDA guidance of less than 5 percent and  
12 consistent with the limit of 1 percent in the proposed  
13 draft ANSI guidance.

14           As shown on the previous summary of  
15 safety, this slide specifies the safety parameters  
16 evaluated following the CK procedure and we will  
17 provide additional detail in each of these parameters  
18 beginning with preservation of best corrected acuity.  
19 The limits established in FDA guidance for  
20 preservation of best corrected acuity are a loss of  
21 more than two lines of BSCVA in less than 5 percent of  
22 eyes and a decrease to worse than 20/40 of less than  
23 1 percent in those eyes with pre-op BSCVA of 20/20 or  
24 better.

25           In addition to the limits established by

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1 FDA guidance, we are also reporting loss of BSCVA of  
2 two lines and BSCVA worse than 20/25 for eyes with  
3 pre-op BSCVA of 20/20 or better. As you can see from  
4 this slide in the CK study, loss of best corrected  
5 acuity was very low across each measure of this  
6 parameter. A loss of more than 2 lines of BSCVA was  
7 reported for only 1 percent of eyes from the 3-month  
8 visit. By 12 months, no eye had this level of loss of  
9 BSCVA. None of the study eyes had best corrected  
10 acuity worse than 20/40 on any of these visits.

11 Of the eyes with BSCVA 20/20 or better at  
12 baseline, 1 percent at BSCVA worse than 20/25 at 6 and  
13 9 months, but none was worse than 20/25 at 12 months.

14 If we look specifically at the population  
15 of eyes which lost 2 or more lines of BSCVA over the  
16 course of the study, you can see that the majority of  
17 these eyes had best corrected acuity of 20/32. No  
18 eyes had BSCVA worse than 20/40.

19 I will now turn the podium over to Peter  
20 Hersh who will present information related to induced  
21 cylinder.

22 DR. HERSH: Thank you, Marguerite. Mr.  
23 Chairman, Panel Members, I'm Dr. Peter Hersh and I  
24 serve as a principal investigator for the conductive  
25 keratoplasty clinical trial. My goal in this section

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1 is to present data on induced cylinder following the  
2 CK procedure.

3 FDA's guidance states that less than 5  
4 percent of eyes are allowed to have an increase from  
5 baseline of greater than 2 diopters of cylinder. We  
6 will also report the incidents of induced cylinder  
7 greater than 1 diopter since this is the limit  
8 reported in labeling for all refractive surgery  
9 devices used in the treatment of hyperopia.

10 Finally, at FDA's request, we will report  
11 a similar analysis using a stratification of greater  
12 than or equal to 1 diopter of induced cylinder.

13 Since concerns have been raised regarding  
14 induced cylinder following conductive keratoplasty,  
15 and since we will be addressing these with a number of  
16 analyses, I first wanted to provide you with a summary  
17 of this information. First, you will see that the  
18 incidents of induced cylinder after CK meets the  
19 current FDA limit of less than 5 percent of eyes with  
20 greater than 2 diopters of induced cylinder. The  
21 cylinder decreases significantly over time and  
22 resolves in a large proportion of the eyes.

23 In eyes with induced cylinder, there was  
24 on average one line less improvement in uncorrected  
25 visual acuity. However, uncorrected visual acuity

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1 improved over time as the astigmatism resolved.

2 Finally, and importantly, best spectacle  
3 corrected visual acuity was not affected by induced  
4 cylinder.

5 So let's begin here. As shown in this  
6 slide, the absolute change in refractive cylinder  
7 remained well below the FDA guidance of less than 5  
8 percent of eyes with induced cylinder greater than 2  
9 diopters at all follow-up examinations. From 6 months  
10 on, the proportion of eyes with induced cylinder of  
11 greater than 2 diopters also met the more stringent  
12 proposed limit of less than 1 percent. Whereas, the  
13 frequency of astigmatism was relatively high at the  
14 early examinations, this decreased significantly over  
15 time.

16 The same information on absolute change in  
17 refractive cylinder is also shown here for the cohort  
18 of eyes with all visits through 12 months further  
19 demonstrating that induced cylinder decreases over  
20 time and meets FDA guidelines.

21 In a further effort to understand both the  
22 magnitude and course of astigmatism after CK, we also  
23 examined the mean induced cylinder over time. Here  
24 you can see that the mean induced cylinder decreases  
25 to less than .50 diopter at months 9 and 12 and this

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1 decrease was statistically significant. We also  
2 performed statistical modeling to determine whether  
3 the resolution in induced cylinder over time was  
4 associated with a loss of refractive effect with  
5 regard to historical hyperopia since this obviously  
6 would be of concern.

7 This modeling revealed that the resolution  
8 of induced cylinder was not attributable to regression  
9 of the spherical correction.

10 Next, we attempted to understand the  
11 actual clinical impact of induced cylinder. To do  
12 this, the study population was stratified into those  
13 eyes with greater than 1 diopter of induced cylinder  
14 as compared to eyes with less than or equal to 1  
15 diopter of cylinder.

16 Now as you can see from the slide, there  
17 was no difference between the two groups with regard  
18 to loss of spectacle corrected visual acuity at 12  
19 months. Indeed, there were no eyes in the induced  
20 cylinder group that lost 2 or more lines of best  
21 corrected vision.

22 We also examined of the effects on best  
23 spectacle corrected vision of manifest cylinder  
24 greater than 0.75 diopters combined with an axis shift  
25 of 30 degrees or more which the FDA considers

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1 clinically significant. Eyes with this level of  
2 cylinder and axis shift had no change in spectacle  
3 corrected vision, while there was a loss of lines in  
4 6 percent of eyes in the group with less than 0.75  
5 diopters of manifest cylinder, or no significant axis  
6 shift.

7 In order to evaluate the impact of induced  
8 cylinder now on the efficacy of the procedure, we  
9 performed an analysis comparing mean lines of  
10 improvement in uncorrected visual acuity between eyes  
11 with induced cylinder and eyes with less than or equal  
12 to 1 diopter of induced cylinder. This analysis first  
13 was performed using two stratifications. Induced  
14 cylinder by absolute magnitude and induced cylinder by  
15 vector analysis. As shown here, the mean UCVA in the  
16 induced cylinder group was 20/32 compared with 20/27  
17 in the low cylinder group.

18 Furthermore, in the induced cylinder group  
19 improvement in uncorrected visual acuity was 3.3 lines  
20 compared with an improvement of 4.4 lines in the low  
21 cylinder group. As you can see, results of this  
22 comparison using the stratifications by vector  
23 analysis yielded similar results.

24 In addition, an analysis was performed for  
25 eyes with any increase in cylinder over baseline and

1 axis shifts of 30 degrees or more which was considered  
2 by FDA again to be clinically significant.

3 As shown here, significant shifts in axis  
4 combined with any increase in cylinder from baseline  
5 had minimal effect on uncorrected vision and no effect  
6 on lines of uncorrected visual acuity improvement.

7 These data thus suggest a difference of  
8 approximately 1 line of improvement in uncorrected  
9 visual acuity as a result of induced cylinder of  
10 greater than 1 diopter. But only a minimal effect on  
11 uncorrected vision of any increase in cylinder over  
12 baseline when combined with significant axis shift.

13 To look further into the effect of induced  
14 cylinder on uncorrected visual acuity the change in  
15 uncorrected visual acuity over time was evaluated for  
16 those eyes with induced cylinder of greater than 1  
17 diopter at the 1-month visit. Consistent with the  
18 resolution of induced cylinder over time, uncorrected  
19 visual acuity improved substantially in these eyes  
20 from 1 through 12 months.

21 As shown in this graph, while the  
22 proportion of eyes with uncorrected visual acuity of  
23 20/20 or better was low, 79 percent of eyes had  
24 uncorrected acuity of 20/25 or better by 12 months and  
25 84 percent had uncorrected visual acuity of 20/32 or

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1 better at 9 months.

2 The FDA target of 20/40 or better in 85  
3 percent of eyes was achieved beginning at 3 months  
4 post-operatively.

5 We next wanted to compare uncorrected  
6 acuity of 20/20 or better in eyes with induced  
7 cylinder to the eyes with less cylinder at 1 month.  
8 The light blue bars that you see here show the low  
9 cylinder group at 1 month, whereas the dark blue bars  
10 represent the induced cylinder group. Consistent with  
11 the resolution of induced cylinder over time,  
12 uncorrected visual acuity improved substantially in  
13 time for both groups and the proportion of eyes  
14 achieving UCVA of 20/20 or better was similar for both  
15 groups at 12 months.

16 The same comparison of eyes with induced  
17 cylinder versus eyes with less cylinder is now shown  
18 here for uncorrected visual acuity of 20/25 or better.  
19 As you can again see from this slide, the proportion  
20 of cylinder eyes with uncorrected vision of 20/25  
21 reached 50 percent at 3 months and there was virtually  
22 no difference between groups in uncorrected visual  
23 acuity at 9 months and at 12 months.

24 Now finally, when looking at uncorrected  
25 vision of 20/40 or better, the low and the high

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1 cylinder groups are very closely matched from 3 months  
2 forward with virtually no difference in uncorrected  
3 visual acuity. The FDA target of 85 percent at 20/40  
4 or better was achieved at 3 months for both groups.

5 Now we're going to shift gears a little  
6 bit and look at the data a somewhat different way.  
7 FDA expressed an interest in looking at eyes with  
8 greater than or equal to 1 diopter of induced cylinder  
9 rather than simply greater than 1 diopter of induced  
10 cylinder and comparing these eyes to less than 1  
11 diopter of induced cylinder. So we're dealing here  
12 with a different stratification.

13 Consistent with the previous comparison,  
14 using the induced cylinder stratification of greater  
15 than 1 diopter there was no significant difference in  
16 the loss of spectacle corrected vision between these  
17 two groups.

18 As before, we again performed an analysis  
19 comparing mean lines of improvement in uncorrected  
20 visual acuity between eyes with induced cylinder and  
21 those with less induced astigmatism. Here again, the  
22 data suggests approximately a difference of 1 line  
23 less improvement in uncorrected visual acuity in the  
24 induced astigmatism group and again no effect on  
25 uncorrected visual acuity when you look at a group of

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1 manifest cylinder greater than 0.75 diopters combined  
2 with an axis shift of 30 degrees or more.

3 Change in uncorrected vision over time was  
4 also evaluated for the eyes with one or more diopters  
5 of induced cylinder at one month. Again, consistent  
6 with resolution of induced cylinder over time,  
7 uncorrected acuity improved substantially through the  
8 12-month follow-up.

9 Finally, to complete the examination of  
10 the impact of induce cylinder after CK we looked at  
11 those eyes with induced cylinder at 1 year. Of the  
12 total population of eyes at 1 year, there were 203; 25  
13 had 1 or more diopters of induced cylinder and 13 eyes  
14 had greater than 1 diópter of induced cylinder. Of  
15 these, 21 of the 25 and 9 of the 13, respectively,  
16 were treated with the current nomagram and therefore  
17 could be evaluated for effectiveness. But first  
18 turning to safety, let's look at best spectacle  
19 corrected visual acuity.

20 Looking at safety, best corrected visual  
21 acuity was very similar for the two groups of eyes  
22 with induced cylinder. The UCVA was 20/32 or better  
23 for all eyes and all by one eye had best spectacle  
24 corrected visual acuity of 20/25 or better.

25 Looking now at uncorrected visual acuity,

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1 there was a substantially lower proportion of eyes  
2 with uncorrected vision at the 20/20 and 20/25 levels  
3 in the presence of induced cylinder compared with eyes  
4 with less cylinder. However, the proportion of eyes  
5 with uncorrected vision, 20/40 or better, was 81  
6 percent for eyes with 1 diopter or more of induced  
7 cylinder approximating the FDA guidance target.

8 Finally, let's look at the astigmatism  
9 outliers at 12 months. A total of 9 eyes treated with  
10 the current nomogram had induced cylinder greater than  
11 1 diopter at 12 months. This listing presents the  
12 uncorrected and best corrected acuities as well as the  
13 satisfaction grading for these outlier eyes.

14 As you can see, post-operative, spectacle  
15 corrected visual acuity was 20/25 or better for all of  
16 these eyes and the majority of eyes, indeed, had  
17 spectacle corrected visual acuity of 20/20 or better.  
18 Uncorrected visual acuity was 20/32 or better in 6 of  
19 the 9 eyes, whereas the remaining 3 eyes had UCVA of  
20 20/50.

21 It's of interest to note that 5 of the 9  
22 eyes were satisfied or very satisfied with the  
23 procedure and 2 were neutral. One was dissatisfied  
24 and finally, one was very dissatisfied. Overall then,  
25 as you can see, uncorrected visual acuity and best

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1 spectacle corrected vision, even in these outliers,  
2 was quite good.

3 In summary then the incidents of induced  
4 cylinder reported in the CK clinical trials meets the  
5 current FDA limit of less than 5 percent of eyes with  
6 greater than 2 diopters of induced cylinder as well as  
7 the more stringent limit of less than 1 percent which  
8 has been identified in the draft ANSI guidance. The  
9 frequency and the magnitude of induced cylinder  
10 decreased significantly over time, resolving in a  
11 large proportion of the eyes.

12 Importantly, this resolution of induced  
13 cylinder was not attributable to regression of the  
14 spherical correction.

15 Induced cylinder assessed by absolute  
16 magnitude, vector analysis and in conjunction with  
17 access shift was associated with approximately one  
18 line less improvement in uncorrected visual acuity.  
19 UCVA in these eyes improved over time as the induced  
20 cylinder resolved.

21 Finally, induced cylinder had virtually no  
22 effect on best corrected visual acuity, irrespective  
23 of the analyses performed and therefore does not raise  
24 any safety concerns.

25 Thank you very much. Dr. McDonald will

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1 now continue with her presentation of the safety and  
2 effectiveness data.

3 DR. McDONALD: Thanks, Peter. Other  
4 safety parameters evaluated included endothelial cell  
5 loss, patient symptoms, complications and adverse  
6 events.

7 Specular microscopy, using the noncontact  
8 Conan Robocon was performed on a subgroup of eyes  
9 enrolled in the CK study and endothelial cell density  
10 was analyzed for images obtained centrally,  
11 mid-peripherally and peripherally. As shown in this  
12 slide, endothelial cell density remained relatively  
13 constant over the course of follow-up from baseline to  
14 3, 6 and 12 months in all regions evaluated.

15 The percentage change in endothelial  
16 density was similarly constant over the course of  
17 follow-up with no changes observed in any of the  
18 regions evaluated. This absence of any change in  
19 endothelial cell density or morphology over the course  
20 of follow-up, irrespective of the region examined,  
21 establishes the safety of radio-frequency energy  
22 delivered to the cornea via the keratoplast tip.

23 Analysis of patient symptoms in  
24 determination of the clinical importance of reported  
25 symptoms, presented a reporting challenge since no

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1 limits had been established by the FDA. Nor are there  
2 standards for collecting and reporting these data.

3 In the absence of pre-established limits,  
4 we have utilized a level suggested by FDA during  
5 review of our PMA, an increase of 5 percent or more in  
6 moderate to very severe symptoms.

7 A subjective questionnaire was  
8 administered to all study patients pre-operatively and  
9 at follow-up examinations. Patients were asked to  
10 rate each of the symptoms listed on this slide as  
11 either none, mild, moderate, marked or very severe.

12 As mentioned, FDA indicated an interest in  
13 subjective symptoms which increased from baseline  
14 levels by 5 percent or more in the categories of  
15 moderate, marked or very severe. The symptoms which  
16 met this criteria are highlighted on this slide and  
17 include dryness, glare, halos, double vision and  
18 changes in vision.

19 The actual incidents reported for each of  
20 these symptoms is shown here. Again, this represents  
21 those symptoms for which a 5 percent increase from  
22 baseline and moderate and marked symptoms was  
23 reported. It is noteworthy, that there was no  
24 significant increase in the very severe rating for any  
25 symptom.

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1                   When considering the actual percentage  
2                   increase in the moderate and marked symptoms listed  
3                   here in detail, it can be observed that all symptoms  
4                   reported as moderate had an increase of 5 to 7  
5                   percent, thus just exceeding the threshold of 5  
6                   percent identified by the FDA as clinically relevant.

7                   More importantly, the increase in marked  
8                   symptoms reported at 6 months decreased at 9 and 12  
9                   months and as previously noted, there was no  
10                  significant increase in the very severe rating for any  
11                  symptom at any time during the study.

12                 The final component to be evaluated for  
13                 safety is reports of complications and adverse events.  
14                 FDA guidance limits the occurrence of adverse events  
15                 to not more than 5 percent of eyes, with any single  
16                 adverse event occurring in less than 1 percent of eyes  
17                 during the study.

18                 Information on complications and adverse  
19                 events was collected at each study visit, using the  
20                 extensive lists of reportable events identified in FDA  
21                 guidance. As you can see from this slide, the  
22                 complication rate for the study was very low, with  
23                 only a small number of complications reported at any  
24                 time during the study.

25                 Further confirmation of the safety of the

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1 CK is provided by the low incidence of adverse events.  
2 There were only three device or procedure-related  
3 events. In one case, a corneal perforation occurred  
4 during the procedure. Investigation revealed that the  
5 glue bond attaching the Teflon top to the CK tip was  
6 fractured from a lateral force which may have occurred  
7 during removal from packaging allowing the stop to  
8 separate from the tip. This subject was subsequently  
9 treated and has had excellent outcomes with  
10 uncorrected acuity of 20/16 at 12 months.

11 Random sampling and testing of keratoplast  
12 tips indicates that this occurrence is not design or  
13 manufacturing-related and was an isolated event. To  
14 prevent further possible occurrences, additional  
15 instructions have been added for the surgeon regarding  
16 the safe removal of the keratoplast tip from its  
17 packaging.

18 In two cases, no energy was applied during  
19 the initial treatment. In both cases, an internal  
20 connection was found to have a poor solder joint,  
21 resulting in no delivery of radio-frequency energy.  
22 A design change to address this was developed and  
23 tested and has been implemented following review by  
24 the FDA. This design modification has prevented any  
25 additional occurrences.

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1           Of the two eyes that were affected by this  
2 complication, one was successfully treated 3 weeks  
3 later. The second eye was determined to be illegible  
4 for participation in the study, due to narrow angles  
5 and was therefore exited from the study.

6           Other adverse events are summarized in  
7 this slide, including IOP greater than 25 millimeters  
8 of mercury in 3 eyes of 2 patients; 1 eye with mild  
9 iritis; a retinal break that was successfully treated  
10 with argon laser; and a decrease in BSCVA secondary to  
11 optic atrophy and inferior attitudinal hemianopsia.

12           Several non-ophthalmic events were also  
13 reported including cancer, heart attack, temporal  
14 arteritis, and miscellaneous other unrelated events.

15           This slide summarizes the safety outcomes  
16 following CK and as we've seen from the data presented  
17 to this point, the study outcomes meet all limits  
18 identified in FDA guidance.

19           Summary and indications for use. To  
20 summarize the effectiveness data presented, the study  
21 results for uncorrected visual acuity and accuracy of  
22 the refractive outcome exceeded FDA targets for  
23 accuracy of MRSE and uncorrected visual acuity.  
24 Furthermore, from the 6-month examination, change in  
25 MRSE was less than or equal to a .50 diopter for 85

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1 percent of the study population and the mean in MRSE  
2 change per month was small, 0.03 diopters to 0.04  
3 diopters for a total mean change of less than a .50  
4 diopter per year. Ninety-four percent of the intended  
5 correction remains at 12 months by a matched pair  
6 analysis. This is compelling effectiveness data  
7 considering that no re-treatments were performed in  
8 this study.

9 All safety limits established by the FDA  
10 and the study protocol were achieved in the study  
11 population. Specifically, all criteria related to the  
12 preservation of BSCVA were met. With regard to  
13 induced cylinder, the proportion of eyes with more  
14 than 2 diopter was below the FDA target throughout the  
15 course of the study and induced cylinder decrease in  
16 frequency and magnitude over time. There was no  
17 effective induced cylinder on BSCVA and the effective  
18 induced cylinder on UCVA was reflected largely in the  
19 slightly lower proportion of eyes with UCVA 20/20 or  
20 better.

21 Finally, the incidence of adverse events  
22 was very low and all resolved without sequelae.

23 On this basis, we respectfully request  
24 that this Advisory Panel renders an approval  
25 determination for this PMA for the conductive

1 keratoplasty procedure with the following indication  
2 for use: CK treatment for the reduction of spherical  
3 hyperopia in the range +0.75 to +3.25 diopters of  
4 cycloplegic spherical hyperopia; -0.75 diopters or  
5 less of refractive astigmatism; +0.75 to +3.00  
6 diopters cycloplegic spherical equivalent; in patients  
7 with less than or equal to .50 diopter difference  
8 between pre-op, manifest and cycloplegic refractions;  
9 in patients 40 years of age or older. The magnitude  
10 of correction diminishes over time with an average  
11 loss of approximately 6 percent by MSRE paired  
12 analysis of the intended correction at 1 year. The  
13 proportion of intended correction retained beyond 12  
14 months is undetermined.

15 Thank you for your time and attention.

16 DR. SUGAR: Does that end the sponsor's  
17 presentation? Please stay at the table then. We are  
18 running ahead of time and what we will do is continue  
19 -- the program has lunch designated at noon. We still  
20 intend to do that, but we will move head. First,  
21 we'll have the Panel questions for the sponsor and  
22 then we will try to move ahead with the FDA  
23 presentation, if we can, prior to lunch.

24 So questions? Dr. Pulido?

25 DR. PULIDO: Yes, thank you very much.

1 Jose Pulido. Thank you very much for a very nice  
2 presentation and I'm sure that my colleagues will be,  
3 from what I've been reading, will be delving into the  
4 statistics, so my question isn't in the statistics.  
5 My questions are first, the safety of radio-frequency  
6 energy in patients with pacemakers or cochlear  
7 implants.

8 DR. GORDON: It's a contraindication. We  
9 were looking back to the Refractec technical --

10 MS. THORNTON: Can you identify yourself,  
11 Judy, and speak into the microphone?

12 DR. GORDON: I apologize. Judy Gordon and  
13 we were referring to Refractec technical personnel who  
14 were here and who have communicated that those  
15 patients would be contraindicated for this treatment.

16 DR. PULIDO: Okay, because that wasn't in  
17 the contraindications and these are elderly patients  
18 and these are the people that will have pacemakers and  
19 cochlear implants. And so that needs to be put in  
20 there if it ultimately will be accepted.

21 DR. GORDON: That can be corrected in the  
22 labeling.

23 DR. PULIDO: Secondly, slide 22 and slide  
24 79 alluded to a patient that was supposed to have  
25 originally received the treatment, but first the

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1 machine wasn't working and then it was determined the  
2 patient had narrow angles and therefore did not  
3 receive treatment. That wasn't one of the  
4 contraindications and yet, you said well, he didn't  
5 receive it because the patient had narrow angles and  
6 therefore it was determined that that was  
7 contraindication. So are you saying narrow angles is  
8 a contraindication?

9 DR. GORDON: Judy Gordon again. Narrow  
10 angles is not a labeling contraindication, but it was  
11 an exclusion criterion identified in the entry  
12 criteria for the study population, so that patient was  
13 inappropriately enrolled, meaning it would have been  
14 a protocol deviation if the patient had been  
15 successfully treated, but in re-screening the patient  
16 after the initial failed treatment to re-perform  
17 another baseline examination, it was determined that  
18 the patient was not eligible and should not have been  
19 enrolled in the first place and so the patient was  
20 discontinued without treatment.

21 DR. PULIDO: How many patients enrolled  
22 did have narrow angles and how can you be sure that  
23 that is not a contraindication?

24 DR. GORDON: I think the issue of narrow  
25 angles on a hyperopic population, particularly in the

1 studies, the refractive surgery studies of hyperopia  
2 really relate to at least in part the number of  
3 cycloplegic refractions that are required in the  
4 post-operative period and the risks therein of the  
5 cycloplegia and so it's pretty typical to exclude  
6 those patients from these studies, but I think it  
7 doesn't necessarily imply that it would be an  
8 appropriate contraindication, but I'll rely on my  
9 clinical advisors here to add commentary on that.

10 DR. McDONALD: I think that, as with all  
11 studies --

12 DR. SUGAR: Again, please identify  
13 yourself, Marguerite.

14 DR. McDONALD: Dr. Marguerite McDonald.  
15 As with all studies, we were trying to just have the  
16 cleanest possible entry criterion be exceedingly  
17 careful. Judy's comment is correct that we  
18 cyclopleged the patients repeatedly, so we were a  
19 little worried there and also you know, we really don't  
20 know what happens to the peripheral profile. Just to  
21 be extra careful. I really don't think the angle  
22 would be affected, but just to be extra careful in the  
23 study. We excluded them.

24 DR. PULIDO: Right. But again, is there  
25 -- I don't have any indication from what I've read

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1 that there isn't a change to the peripheral profile  
2 into the trabeculum meshwork.

3 I thought maybe you would have data  
4 otherwise that I wasn't able to find.

5 DR. DURRIE: This is Dan Durrie and I've  
6 been involved in several of these studies and there  
7 hasn't been any evidence in any collagen shrinkage  
8 procedure that there is narrowing, but there's not a  
9 good way, we didn't do ultrasonic measurements.  
10 There's just not a good way to measure it.

11 Being involved in the design of these  
12 studies it's exactly true what Judy has said. This  
13 really is a contraindication in the study because  
14 we're going to cycloplege these patients multiple  
15 times and that has really been the contraindication on  
16 putting patients in, but there's nothing in this study  
17 or other ones that I've been involved in that are  
18 shown that the angle structure is changed with  
19 collagen shrinkage procedures and periphery.

20 DR. PULIDO: One other question that I had  
21 and that relates to patients, patient number -- the  
22 hospitalization for tonsillectomy an nasal septum  
23 repair. Now it lists that -- if you could turn to --  
24 is it Volume II, page 191 and in it, it has the  
25 manifest refraction at the 6-month visit with -2.00,

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1 -0.75 at 20 in the right eye and plano -0.5 at 165 in  
2 the left. So this patient had, if he or she was very  
3 hyperopic, a marked myopic shift.

4 We don't have her pre-op refraction. What  
5 was it?

6 DR. GORDON: We can look that up. Judy  
7 Gordon. We'll have to pull that information.

8 DR. PULIDO: I'd like to know what that  
9 was.

10 DR. GORDON: We'll get to you in a few  
11 minutes with that information.

12 DR. SUGAR: The issue being?

13 DR. PULIDO: The issue being just want to  
14 make sure the patient was properly enrolled in the  
15 study.

16 DR. SUGAR: Are there other questions for  
17 the sponsor?

18 Go ahead, Dr. Matoba, and then Dr.  
19 Grimmett.

20 DR. MATOBA: I would expect, this is Alice  
21 Matoba. I would expect some increase in intraocular  
22 pressure immediately following the procedure since you  
23 were causing shrinkage of collagen. I wondered if you  
24 had taken an IOPs and if you had some idea of what the  
25 magnitude of the change might be?

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1 DR. GORDON: Judy Gordon. Intraocular  
2 pressure measurements were made at every examination,  
3 including post-operative Day 1 and there was no  
4 evidence of any change. We can show you the --

5 DR. MATOBA: Actually, I'm talking about  
6 acutely, immediately after the procedure, I would  
7 expect a rise in pressure.

8 DR. GORDON: Measurements were not made in  
9 the first 24 hours.

10 DR. MATOBA: Okay. And then my second  
11 question is in terms of your endothelial cell loss  
12 data which looked great, the n was only 162 and that  
13 subsequent patients, I wondered what the treatment  
14 parameters were if you had enough patients who had the  
15 32 spot or the higher level of treatment in those  
16 patients?

17 DR. GORDON: Judy Gordon. That's an  
18 excellent question and we'll take a look at that, but  
19 again, I can't answer without looking.

20 DR. MATOBA: Okay, then my third question  
21 is in regard to patient satisfaction data. It  
22 appeared to me that as you go towards 12 months the  
23 percentage of patients who were dissatisfied or very  
24 dissatisfied, the combined total appeared to increase  
25 compared to the earlier study points and the n was

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1           only 198 for 12 months. I wonder if that trend toward  
2           slightly increasing percentage of dissatisfied and  
3           very dissatisfied patients holds up, if you look at  
4           more patients or it could increase, continue to  
5           increase over time?

6                     DR. GORDON: Judy Gordon, again. There  
7           tends to be considerable variability in these types of  
8           subjective questions and I will check with the  
9           statistician, but I think that the variances that are  
10          observed in those tables were nonsignificant. We did  
11          some extensive statistical testing there, so we can  
12          check on that, but we haven't seen any trends that  
13          would indicate any change, dramatic change over time.

14                    DR. GRIMMETT: Michael Grimmett. I have  
15          one comment and two questions.

16                    DR. SUGAR: I guess there's a follow-up  
17          comment.

18                    DR. McDONALD: I'm sorry, Marguerite  
19          McDonald. One last thing, the cyclometric testing  
20          pulls different things out. At one year, Dr. Matoba,  
21          95 percent of patients felt that their quality of  
22          vision was improved. Five percent said no  
23          improvement, so those questions pull out different  
24          things, but we will look for you.

25                    DR. GRIMMETT: Mike Grimmett again. One

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1 comment, two questions. I had a similar thought to  
2 Dr. Pulido regarding the pacer issue and I would just  
3 add that the FDA or sponsor consider implantable  
4 defibrillator devices as well.

5 Question. On slide 8 of your presentation  
6 that outlined how the spots are placed on that corneal  
7 marker, for the last 8 spots when you move from 24 to  
8 32, is there any identifying marker or anything how  
9 you pick in between or is it best estimate and how  
10 hard is that to do with precision?

11 DR. McDONALD: Dr. McDonald. That's an  
12 excellent question. The hand-held marker does not  
13 have dashes or elements to indicate the last 8 spots.  
14 If you're doing a maximum treatment of 32, but several  
15 things. The little distance that you're bisecting is  
16 so short, it's very, very easy to dissect it.  
17 Placement doesn't actually matter of the last 8 as  
18 long as you're somewhere on that ring because what  
19 you're doing is cinching the periphery, so even if  
20 you're a tiny bit off on dissecting the short distance  
21 which would be hard to do, you are still  
22 circumferentially shrinking the ring.

23 Last, but not least, if you add more  
24 elements to the marker and then you ink it up with one  
25 of the FDA-approved dyes, you start to get a big blue

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1 smear and you really can't see anything, so that's the  
2 maximum that you can practically put on one marker.

3 DR. GRIMMETT: Thank you. And another  
4 question, I just want to clarify or reconcile some  
5 data in your slides that went by too fast for me to  
6 reconcile it. Slide 64 of Dr. Hersh's presentation  
7 that goes over this cylinder with uncorrected visual  
8 acuity, we have in the latter column eyes with greater  
9 than or equal to 1.00 diopter of induced cylinder and  
10 we see the rates of certain levels of vision, for  
11 example, 29 percent have 20/20 or better.

12 I want to reconcile that with slide 61  
13 that I think is showing the exact same data, trying to  
14 show induced cylinder greater than or equal to 1.00  
15 diopter at various vision levels. The vision level,  
16 at least the way I'm reading it on slide 61 says 20/20  
17 or better in 49 percent. Yet, slide 64 says 20/20 or  
18 better in 29 percent. And the other categories are  
19 different as well. 20/25, slide 64, says 52 percent;  
20 slide 61 says 80 percent at month 12.

21 DR. HERSH: These are --

22 DR. GRIMMETT: Go ahead.

23 DR. HERSH: Dr. Peter Hersh. These are  
24 actually different groups of patients. Slide 61 is  
25 that group of patients who had greater than or equal

1 to 1.00 diopter of cylinder at the 1-month visit. So  
2 all patients who we saw at 1 month, who had greater  
3 than or equal to 1.00 diopter of induced cylinder, we  
4 then followed on for the subsequent visits to look at  
5 the natural history of the induced cylinder.

6 Now slide 64 is a snapshot of the group of  
7 patients who have reached 12 months. So it's simply  
8 the group of patients who have reached 12 months  
9 looking at those with induced cylinder and those  
10 without induced cylinder, so they represent different  
11 patient groups.

12 DR. GRIMMETT: Great. Thank you very  
13 much.

14 DR. SUGAR: I have a question. In terms  
15 of the pattern, you prescribe a pattern of placing the  
16 spots. Was that derived empirically or arbitrarily or  
17 how was it derived?

18 DR. DURRIE: The pattern -- this is Dan  
19 Durrie. The pattern was done off of international  
20 investigation that was done previously and then very  
21 importantly, the first 54 patients that were done  
22 before the nomagram adjustment and I think that that's  
23 why you have a clean group of data done with one  
24 pattern that was evolved not only on international  
25 experience, but then the experience of the first 54

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1 eyes to come up with the suggested patterns.

2 DR. SUGAR: So -- Joel Sugar. So you're  
3 implying that you tested different patterns and this  
4 was the most effective and the pattern does make a  
5 difference? Is that the implication from what you  
6 just said?

7 DR. DURRIE: No. The situation as far as  
8 this particular pattern of only adding one spots and  
9 not changing energy, a lot of those things were looked  
10 at before, but in this particular thing is the only  
11 thing that the surgeon does in which makes this quite  
12 easy is adding an additional number of spots for  
13 higher diopter correction.

14 DR. SUGAR: That, I understand. I'm  
15 talking about the pattern in which they're applied,  
16 given that you decided that you're going to do 24  
17 spots on a patient with 2 diopters.

18 DR. McDONALD: Dr. McDonald. This pattern  
19 was established by the international investigative  
20 team, but it's also the pattern that's been used  
21 historically in the PERK study and other studies  
22 because if, for whatever reason, you have to abort a  
23 procedure in the middle, you will have induced less  
24 cylinder. If you go around from one spot to the next  
25 you could induce a huge amount of astigmatism, if for

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1           whatever reason you had to abort.

2                         DR. SUGAR: Thank you. Dr. Weiss?

3                         DR. WEISS: I had three questions. The  
4 first one was that 80 percent and I think in the  
5 September document, it was indicated that 80 percent  
6 of patients did not need glasses after the procedure.  
7 Considering that two-thirds of patients had 1.9  
8 diopter of hyperopia or less, do you have a percentage  
9 of patients who wore glasses at a distance before the  
10 procedure, so that we can compare the two numbers?

11                        DR. GORDON: Dr. Judy Gordon. No, we did  
12 not collect preoperative spectacle correction usage.

13                        DR. WEISS: Okay. In the list of side  
14 effects patient subjective complaints, mild diplopia  
15 increased from a level of 5 percent pre-op to 14  
16 percent subsequently. Was that correlated with pupil  
17 size or refraction?

18                        DR. GORDON: Judy Gordon. I can speak to  
19 this because I had the pleasure of addressing the  
20 challenge of looking at symptoms that are rated on a  
21 5 point scale about 20 symptoms over 6 visits and so  
22 in trying to do a meaningful analysis of this and  
23 because we had collected pupil diameters, we actually  
24 just did a statistical comparison of an overall type  
25 of symptomatology for smaller pupils versus larger

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1 pupils and we were really gratified to see that there  
2 were no differences observed at all.

3 DR. WEISS: So we don't really know why  
4 they had that complaint of diplopia.

5 DR. GORDON: Correct.

6 DR. WEISS: Finally, this is in regard to  
7 the indications for the procedure. On the last slide,  
8 you indicated that the proportion of intended  
9 correction retained beyond 12 months is not  
10 determined, undetermined, and in the physicians  
11 reference guide it's indicated that there is some loss  
12 of refractive effect with time.

13 Are you not saying that this is a  
14 temporary procedure?

15 DR. GORDON: This is Judy Gordon again.  
16 I think we were attempting to articulate in some  
17 fashion that have a body of information and a clear  
18 understanding of what occurs during the initial  
19 12-month of follow-up, but not beyond and we've  
20 attempted to somehow quantify or semi-quantify to  
21 patients and physicians what proportion of the effect  
22 or the intended effect is retained at 12 months and  
23 for that reason we have suggested the 94 percent  
24 retained. But beyond the 12-month period in the  
25 absence of data, we've added language suggesting that

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1 the continued course of refractive correction is  
2 undetermined.

3 DR. WEISS: Would not the 24-month data,  
4 although limited, give you some more indication as to  
5 what happens in the patients in whom you have 24-month  
6 data?

7 DR. GORDON: Yes, absolutely.

8 DR. SUGAR: Go ahead, Dr. Mathers.

9 DR. MATHERS: Dr. Mathers. I have a  
10 couple of questions. You mentioned something about  
11 that this data was, of course, a single application.  
12 Do you think that there will be for some patients  
13 several applications as there are with other  
14 refractive procedures and how would you approach that?

15 DR. GORDON: Judy Gordon. The purpose of  
16 the study was to evaluate the outcome of a single  
17 procedure and we have no information at this time on  
18 the effects or benefits of additional applications of  
19 spots.

20 DR. MATHERS: And some patients will have  
21 smaller corneas. Was there any exclusion criteria  
22 regarding the size of the cornea and would you have  
23 difficulty in treating more peripheral lesions or  
24 making more peripheral lesions in smaller corners.  
25 Some of these hyperopic people might have smaller

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1 corneas?

2 DR. McDONALD: Dr. McDonald. We did not  
3 measure pre-op corneal diameter, but no one that I'm  
4 aware of, none of the investigators complained that  
5 they had difficulty placing the spots in any of the  
6 corneas.

7 DR. SUGAR: Dr. Matoba?

8 DR. MATOBA: In your presentation you  
9 stated that the induced cylinder resolved over 12  
10 months, but your spherical induced change was stable  
11 and why do you think that is?

12 DR. HERSH: It seems to be a wound-healing  
13 effect that we really see in all refractive surgery  
14 procedures that we do. Wound remodeling, particularly  
15 epithelial remodeling has been shown in any number of  
16 procedures we do now, PRK lasik tend to resolve  
17 astigmatism in topography abnormality over time and I  
18 would suspect that it's a similar case here where  
19 wound healing particularly, possibly epithelial  
20 remodeling diminishes the cylinder and we so retain  
21 the spherical effect.

22 DR. SUGAR: Go ahead, Dr. Bradley.

23 DR. BRADLEY: Dr. Bradley. In a lot of  
24 the statistics you just presented, the most troubling  
25 case was the 1-month data set where some of the FDA

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1 marks were not met. It makes me wonder what happened  
2 prior to 1 month. Do you have data collected during  
3 that period, particularly I'm interested in the  
4 manifest refractive error, the uncorrected visual  
5 acuity and best spectacle visual acuity. And my  
6 concern, of course, is that the patient will be  
7 suffering some, albeit temporary, visual disability  
8 due to the procedure.

9 DR. GORDON: Judy Gordon. The standards  
10 for reporting in these refractive surgery studies is  
11 pretty much what we've shown and so uncorrected acuity  
12 is manifest and we also performed cycloplegic  
13 refractions to have more confidence in our outcomes  
14 were collected and were reported at 1, 3, 6, 9 and 12  
15 months.

16 We'll have further discussion later  
17 relative to some additional comments in labeling and  
18 we've shown that the uncorrected acuities, given the  
19 initial overcorrection could lead to some challenges  
20 in uncorrected vision. None of the patients in the  
21 studies, either requested or required spectacle  
22 correction during the early period, but we'll propose  
23 labeling to suggesting that that may be a concern and  
24 that physicians and patients should be aware of that.

25 DR. BRADLEY: Can I just come back on

1 that?

2 DR. SUGAR: Dr. McDonald wanted to further  
3 respond.

4 DR. BRADLEY: Can I just clarify  
5 something? You didn't answer the question. I asked  
6 you if you had any data prior to one month. You've  
7 just told me you presented the 1-month data which I've  
8 seen, of course. I'll repeat the question. Do you  
9 have any data prior to one month?

10 DR. GORDON: I'll have to check and find  
11 out. I think that we don't.

12 DR. McDONALD: Dr. McDonald. Dr. Bradley,  
13 we looked at the people at one month who had an MSRV  
14 of -1.00 or worse. Also, the people who at one month  
15 were 20/40 or worse than 20/40 uncorrected. In the  
16 first group, the people with an MSRE of -1.00 or  
17 greater at one month, that was 23 percent of the  
18 population, 81 eyes. Six patients had same day  
19 bilateral in that group. Of the six patients, two  
20 were very satisfied, two were satisfied, two were  
21 neutral, but none were dissatisfied or very  
22 dissatisfied. At one month, the 21 percent, n equals  
23 73, who had worse than 20/40 uncorrected. There were  
24 nine patients same day bilateral. Three of the nine  
25 were very satisfied, three of the nine were satisfied,

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1 and three of the nine were neutral and no one was  
2 dissatisfied or very dissatisfied. So although they  
3 are briefly, either as a percentage of the population,  
4 almost a quarter that are briefly more myopic or have  
5 worse than driving vision, they are not dissatisfied  
6 or very dissatisfied.

7 DR. BRADLEY: If I could just comment on  
8 that. In some ways it seems reassuring, but to me it  
9 seems quite alarming that the criteria of 20/40 that  
10 we are holding out as being so important you find  
11 those people who have worse than 20/40 are quite  
12 satisfied. Likewise, people who are 1.00 or more  
13 diopter myopic are satisfied and makes one wonder how  
14 to interpret the satisfaction data.

15 DR. McDONALD: Dr. McDonald. I think  
16 they're well aware that it's temporary and I think  
17 that's the key to their satisfaction.

18 DR. SUGAR: Dr. McMahon and then Dr.  
19 Weiss.

20 DR. McMAHON: Tim McMahon. There was no  
21 data presented in your presentation and only minimal  
22 data presented in supplemental submission with regard  
23 to the near vision.

24 DR. SUGAR: Is that microphone on?

25 DR. McMAHON: Yes. Let me repeat that.

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1 Tim McMAhon. There were two graphs presented in the  
2 red book with regard to near vision. My question is  
3 two-fold. One is can you describe your methodology  
4 for correcting for best corrective near vision and how  
5 that was measured?

6 DR. GORDON: Judy Gordon. Perhaps I can  
7 just comment. Because near vision was not identified  
8 as a primary outcome in this study, we have concerns  
9 in evaluating the data as we were preparing the PMA in  
10 the rigor of the method and there was inconsistency in  
11 the near cards used, so we don't feel it would be the  
12 basis for any claims. It can give us an indication  
13 though of what did occur and that is that we did not  
14 see any effect of conductive keratoplasty on best  
15 corrected near acuity and there was a pretty  
16 substantial improvement in near uncorrected visual  
17 acuity from pre-op where about 4 percent of eyes had  
18 Yager\* 3 or better and that improved to about 40  
19 percent. We could show you that data. It's in one of  
20 the later submissions to FDA. But again, we were  
21 reluctant to present that and over-represent it in any  
22 way, given that there was not necessarily an adequate  
23 level of standardization of the methodology for  
24 collecting the information.

25 DR. McMAHON: All right, the second one is

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1 help me get over my amazement that a substantial  
2 percentage of the patients had induced cylinder and/or  
3 shifts in cylinder axis with this procedure, yet the  
4 percentage of patients who had excellent best  
5 corrected acuity seems to defy logic to me.

6 When you have a focal procedure that  
7 affects local areas of the cornea, it seems to me that  
8 it would be nearly possible not to have a substantial  
9 increase, the amount of irregular astigmatism, yet  
10 with a very high percentage of patients having best  
11 corrected acuity of 20/20 or close to that, it implies  
12 an orthogonal or regular astigmatism. Can you help me  
13 explain how that is? To me, that just doesn't wash.

14 DR. DURRIE: This is Dan Durrie. You  
15 really bring up an important point and that's why I  
16 wasn't very impressed with this data, is that this is  
17 best corrected spectacle acuity and you would expect  
18 if it was irregular astigmatism that they would be  
19 losing best corrected vision and in this particular  
20 procedure, we have seen that the astigmatism deduced  
21 was at least correctable with spectacles and it did  
22 not have the induced or regular astigmatism you expect  
23 from focal correction. So I think the data really  
24 speaks for itself is the fact that we can't correct  
25 regular astigmatism with spectacles. We know that.

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1 And the fact that we did preserve best corrected  
2 vision I think is a sign that the irregular  
3 astigmatism was very small.

4 DR. McMAHON: Do you have topography data  
5 with this data set?

6 DR. HERSH: I've done a few analyses  
7 simply on my own patients and can't comment on the  
8 entire patient set. We did not find any correlations,  
9 thus far, with topography and a number of outcomes.  
10 We looked at procedure centration which indeed was  
11 quite good and that showed no correlation with any  
12 outcomes including induced astigmatism. We looked at  
13 loss of spectacle-corrected vision and again, did not  
14 find a correlation. Indeed, the topography,  
15 anectdotally, look good and the kind of irregularities  
16 that one might see or one saw in PRK, for instance,  
17 during the wound healing phase didn't really again, in  
18 my patient subset, appear to obtain. So potentially  
19 working in the periphery, rather than removing tissue  
20 essentially gives you a more regular response and the  
21 wound healing effects that could lead to irregular  
22 topography might be precluded in a peripheral  
23 technique like this.

24 DR. McMAHON: Thank you.

25 DR. SUGAR: Okay, Marguerite and then Dr.

1 Bradley.

2 DR. McDONALD: Marguerite McDonald. Just  
3 to add a little more to that comment, I think working  
4 in the far periphery is the key and whenever we've  
5 seen a hand-held procedure very close to the visual  
6 axis like hexagonal keratotomy, the incidence of  
7 irregular astigmatism goes sky high. So I think it's  
8 the fact that we're out in the far periphery.

9 DR. SUGAR: Dr. Bradley, then Dr. Huang  
10 and then Dr. Jurkus and then Dr. Grimmett.

11 DR. BRADLEY: It's sort of a carry-on  
12 question from Dr. McMahon's question. If I recall in  
13 the data, the subjects who had the largest amount of  
14 induced astigmatism did have slightly lower best  
15 spectacle corrected visual acuity. Perhaps you could  
16 either confirm or deny that. If that is the case, my  
17 interpretation was, in fact, that along with  
18 astigmatism, which we are calling regular astigmatism,  
19 there was some induced irregular astigmatism, which  
20 was not correctable by the spectacles and in the  
21 modern parlance I think we might refer to that as some  
22 higher order aberration, probably kerma which one  
23 might imagine from some hand-held device which doesn't  
24 have precise positioning. But I may have misrecalled  
25 the data. Can anyone confirm or deny what I just --

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1 DR. SUGAR: I thought that they showed  
2 that the acuities were actually quite similar. I'm  
3 waiting really for them to give their own data.

4 DR. BRADLEY: Then we can forget what I  
5 just said if it's the same, but I thought I remember  
6 seeing them differently.

7 Dr. Weiss is suggesting that maybe my  
8 recollection is from the original data set and not the  
9 revised data set.

10 Perhaps if you could just check on that  
11 anyway, but the idea being -- you're right, if it is  
12 correctable with spectacle lenses, remarkably the  
13 induced cylinder is just that, it is induced  
14 astigmatism whereas we might have imagined that the  
15 measured induced astigmatism is just one component of  
16 a myriad of aberrations that are induced by the  
17 procedure, and therefore we would imagine that some of  
18 these would not be correctable with something we call  
19 correcting lens and therefore we would imagine those  
20 with large amounts of induced astigmatism would  
21 presumably have larger amounts of other aberrations  
22 which would not be correctable and therefore best  
23 spectacle corrected visual acuity would not quite be  
24 as good in that group.

25 DR. SUGAR: Is there a comment from the

1 sponsor? Okay, Dr. Huang?

2 DR. HUANG: Andrew Huang. My concerns the  
3 long-term stability of your results. From 6 to 9  
4 months the regression was .09 diopter and from 9 to 12  
5 months the regression is .12 diopter. Do you have any  
6 evidence suggesting that this rate of regression is  
7 stabilized after one year of follow-up or do you think  
8 the data in whatever, 24 months, patients you have  
9 collected suggesting that this rate of regression is  
10 progressive?

11 DR. GORDON: We have 24-month data and  
12 updated 12-month data that's been submitted to FDA as  
13 we indicated, but they were submitted quite recently,  
14 not in anticipation of planning for this Panel  
15 meeting. So we had no plans to show those data, but  
16 we can comment that in a very small number of eyes  
17 with data through 24 months, the rate of change is  
18 quite small, between 12 and 24 months, but it's a very  
19 small population and for that reason we've taken the  
20 position in our proposed labeling that the loss or the  
21 change in refractive effect after 12 months is  
22 undetermined at this point in time, based on the data  
23 that you have reviewed.

24 DR. SUGAR: Dr. Jurkus, I think is next.

25 DR. JURKUS: My question goes to the

1 patient satisfaction from draft 1 of pages 26 and 27.  
2 And in looking at them it appears that 1 in 3 people  
3 showed an increase of some sort in complaints of  
4 halos, fluctuation in vision and variation in dim  
5 vision from pre-operative to post-operative. And to  
6 me, this seems like quite a large amount of increase.

7 Is there any correlation to pupil size or  
8 to power or reasons why that, again, 1 in 3 would say  
9 that they have more problems with halos and  
10 fluctuation in vision after surgery than they did  
11 before?

12 DR. GORDON: I think there's two separate  
13 issues here. One is, as I mentioned before, we did do  
14 a very thorough statistical analysis relative to pupil  
15 size because obviously that would be a concern that  
16 one would want to label for and we did not see any  
17 effect of pupil size on symptoms. The other comment  
18 is more general and that, as I mentioned, we collect  
19 information on a scale, a 5-point scale of 0 to 5 at  
20 six periods in time and for about 20 symptoms. So you  
21 tend to see all kinds of changes all over the place.  
22 For that reason, as we struggle to somehow define what  
23 would be considered clinically relevant we came up  
24 with an -- FDA had suggested looking at a greater than  
25 or equal to 5 percent increase in the categories

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1 beyond mild, so the marked, moderate and very severe.  
2 You see the biggest changes over time in both  
3 directions and across these types of studies in the  
4 mild where you just get a lot of people marking these  
5 things on these forms. You get the sense of, if you  
6 look at these individually as I have over a number of  
7 studies and I think Dr. Durrie could comment to that  
8 effect as well, so I think the data that we think is  
9 clinically relevant is what we showed in terms of  
10 greater than or equal to 5 percent increase from  
11 baseline and those symptoms that you measured did fall  
12 into that category, although they did improve to some  
13 extent over time.

14 DR. JURKUS: Was there any correlation --  
15 Dr. Jurkus again -- to the amount of correction? Did  
16 the people who had like the +3 people have more  
17 fluctuation than +75 people?

18 DR. GORDON: This is Dr. Gordon again. I  
19 would have to confirm that, but I believe that was not  
20 the case and one of the things that we noted as we  
21 looked at some of the key parameters by dioptric group  
22 was that it was in the higher range of hyperopes, that  
23 we have the higher levels of satisfaction. More  
24 positive, I think it just has to do with more  
25 perceived benefit perhaps, but I don't believe we saw

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1 any difference across dioptric range and symptom  
2 reporting that was at any statistical level.

3 DR. SUGAR: Dr. Grimmett?

4 DR. GRIMMETT: Mike Grimmett.

5 DR. SUGAR: I'm sorry, Dr. Ho hasn't  
6 spoken yet. I'd like to give him an opportunity.

7 DR. HO: Allen Ho. Just a question with  
8 respect to the long-term data. Can you tell me  
9 approximately when the last patient was recruited and  
10 does our lack of 24-month data indicate a fall off in  
11 follow-up compliance or does that indicate that they  
12 have not reached those milestones yet?

13 DR. GORDON: Judy Gordon again. Having  
14 been very close to this study, but not having managed  
15 it myself, I'd have to say and Dr. McDonald commented  
16 that the level of compliance was one of the highest  
17 I've seen, 97 percent. Over 95 percent at each visit.  
18 And the data that we do have available at 24 months is  
19 again 95 percent of the eyes that have hit that  
20 window, but a small number of eyes have gotten to that  
21 point and I'll have to defer to when was the last  
22 patient enrolled, but in any case, we have at every  
23 interval examined accountability because in the  
24 absence of having more than 90 percent of data  
25 available, we have not reported, we would not report

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1 on a parameter, and in all cases wherever we've  
2 reported, we've had more than 95 percent of eyes that  
3 were eligible for the examination come in and be  
4 examined.

5 DR. HO: Allen Ho again. So in other  
6 words, when can we expect to anticipate that the last  
7 enrolled patient will have 24-month data if they come?

8 DR. GORDON: The last patient was enrolled  
9 in December of 2000, so that patient hits one year  
10 shortly and two years in about a year from now.

11 DR. HO: Thank you.

12 DR. SUGAR: And now, Dr. Grimmett?

13 DR. GRIMMETT: Mike Grimmett. I apologize  
14 if this was previously stated or if it's redone --  
15 regarding the 24 patients who lost greater than or  
16 equal to two lines of best corrected vision in 6  
17 months or later, were any of them contact lens  
18 over-refracted as a diagnostic step to rule in a  
19 regular astigmatism?

20 DR. GORDON: Dr. Gordon. We'll find out  
21 and get back to you on that. I don't have the answer  
22 on that.

23 DR. GRIMMETT: Okay.

24 DR. GORDON: We're making a list of  
25 questions.

1 DR. GRIMMETT: Okay, I thought I had  
2 missed it. Sorry.

3 DR. GORDON: We didn't say anything to  
4 that effect.

5 DR. GRIMMETT: Okay.

6 DR. SUGAR: Jayne?

7 DR. WEISS: Jayne Weiss. What did you  
8 find the mean dioptic change was on a monthly basis  
9 between 12 and 24 months in those patients who you do  
10 have data on?

11 DR. GORDON: Judy Gordon. Dr. Rosenthal  
12 is shaking his head in a negative direction, so I'm  
13 hesitating to respond.

14 DR. ROSENTHAL: Dr. Weiss, we normally  
15 have data presented here related to what was presented  
16 in the PMA submission. If the Panel feels that they  
17 require additional data to be looked at by the Agency,  
18 that is one of the things you can consider in your  
19 deliberations.

20 DR. SUGAR: Dr. Bradley.

21 DR. BRADLEY: I just wanted to add a few  
22 comments to Dr. Gordon's reply to Dr. Jurkus' question  
23 about the subjective data. I would concur with Dr.  
24 Gordon that they're very difficult to interpret and  
25 really without an effective placebo group, I really

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1 have a lot of trouble making much of those data in the  
2 sense that there were no alarming signs in the data  
3 set. But being fully aware that there could be huge  
4 biases either plus or minus in that data set, you can  
5 easily imagine that patients who just had something  
6 done to their eye are extremely observant of any  
7 nuance in their sight from that day on and therefore  
8 the reporting of adverse symptoms might go up.

9           Conversely, you can imagine the opposite  
10 bias. They've just committed themselves to an  
11 irreversible surgical procedure on their eyes, so  
12 they're really biased to think good of what they've  
13 just done, so that you can imagine bias going either  
14 way in that data set and I think when, as I think  
15 you've observed and reported quite nicely this  
16 morning, very small changes or what seemed like very  
17 small changes in the reporting, given the potential  
18 for bias either way, it's very difficult to make much  
19 of those. That was my interpretation.

20           DR. SUGAR: Dr. Huang and then we're going  
21 to move in about two minutes into the FDA's  
22 presentation. We also -- do you have answers to the  
23 earlier questions like endothelial cell count? After  
24 Dr. Huang's question, we'll ask for those.

25           Go ahead, Dr. Huang.

1 DR. HUANG: I have two questions regarding  
2 the quality of life issue. Given the fact that  
3 greater than 50 percent of the patient went 6 months,  
4 still have a significant amount of induced cylinder  
5 and a residual undercorrection, and is there any data  
6 suggesting some of the patients may need remedial  
7 service such as contact lenses or spectacle  
8 corrections?

9 DR. DURRIE: This is Dan Durrie. And this  
10 is actually the seventh hyperopic clinical trial that  
11 I'm involved in so I think that one of the things that  
12 I think I'm bringing a perspective of the biases over  
13 multiple studies, but I think it was very interesting  
14 to me in this study is we didn't have -- I personally  
15 did not have a single patient during this time of  
16 overcorrection or induced astigmatism that even asked  
17 for spectacle correction or asked for a retreatment  
18 which has not happened in other clinical trials. So  
19 these patients did not need additional help, did not  
20 request it and I think that that was a lot because the  
21 overshoot was not that great. They were always within  
22 three quarters diopter on average of the plano mean  
23 and also the induced astigmatism did not seem to be  
24 that clinically significant to the patients.

25 You have to remember, these patients, a

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1 lot of them were +1.50, +2.00, +3.00 diopter hyperopes  
2 who were used to some very poor vision. The average  
3 age was 53 and these patients really weren't seeing  
4 very well. Any of you who have gotten hyperopic like  
5 I did over the years understand that. I think that  
6 these patients were not needing any remedial -- not  
7 even spectacles, let alone contact lenses during that  
8 period.

9 DR. SUGAR: Go ahead.

10 DR. McDONALD: Marguerite McDonald. We  
11 pulled some data, proportion of eyes using distance  
12 corrective lenses, eyes treated with current nomogram.  
13 This is 14 percent at 6 months and across all time  
14 points, 80 percent of the eyes and more reported no  
15 use of corrective lenses for distance vision.

16 DR. SUGAR: Did you have --

17 DR. HUANG: Could you repeat that?

18 DR. SUGAR: Could you go ahead and repeat  
19 that?

20 DR. McDONALD: McDonald again. Proportion  
21 of eyes using distance corrective lenses, eyes treated  
22 with current nomogram. This was 14 percent at 6  
23 months and across all time points, 80 percent of eyes  
24 and more reported no use of corrective lenses for  
25 distance vision.

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1 DR. SUGAR: Have you finished with your  
2 question, Dr. Huang?

3 DR. HUANG: That's fine, thank you.

4 DR. SUGAR: Then do you have a response to  
5 the endothelial cell question and the question on  
6 contact lenses?

7 DR. GORDON: Yes. We have a couple of  
8 responses here. First of all, this is Judy Gordon  
9 again. Dr. Pulido asked about a specific patient that  
10 had nasal septal repair. The preoperative manifest  
11 refraction for that eye was +1.75, -1.75 cell. So the  
12 MRSE was 1.3 and the patient was eligible for  
13 enrollment.

14 DR. PULIDO: And then she ended up at  
15 -2.00 for a while?

16 DR. GORDON: That was the 6-month  
17 observation. We'll check. I don't have the full line  
18 listing, but we'll pull that and see what additional  
19 follow-up we may have on that patient. We have almost  
20 all 9-month follow-up at least, so there should be  
21 another examination.

22 DR. PULIDO: That's very predictive.  
23 Thank you.

24 DR. SUGAR: Then the two other.

25 DR. GORDON: With regard to endothelial

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1 cell density, we did not examine those data by  
2 dioptic power. It was a fairly small number of eyes.  
3 It's a sub-study. But we do know that 40 percent of  
4 the eyes are somewhere in that neighborhood, were in  
5 the higher dioptic range at entry, meaning we had a  
6 pretty good distribution of eyes that were greater  
7 than 2, up to 3 and a quarter diopter spherical  
8 hyperopia, so we would anticipate that there would be  
9 a pretty even distribution of those eyes in the  
10 endothelial cell study. And in fact, those eyes were  
11 enrolled in the initial phase of study when we were  
12 enrolling up a baseline CRSE of 4 diopters, so there  
13 should be perhaps even more eyes there that were at  
14 the higher range.

15 DR. SUGAR: Okay, and then the contact  
16 lens question?

17 DR. GORDON: Yes, Judy Gordon again. With  
18 regard to contact lenses, contact lens over-refraction  
19 was required by the study protocol for eyes with best  
20 corrected acuity worse than 20/40 and since all of  
21 these eyes were better than that, 20/32 and 20/25,  
22 there were none performed.

23 DR. SUGAR: Thank you. I'd like to have  
24 the sponsor then move back from the table and have the  
25 FDA group come up and give their presentation.

1 (Pause.)

2 MR. GLOVER: Hi, I'm Joel Glover. I'm the  
3 FDA Team Leader for the application. Since it's  
4 already been introduced, I just have a few brief  
5 comments. First, I want to thank the Panel for  
6 reviewing and discussing the application today. I  
7 want to thank the sponsor for being so responsive  
8 during the rest of the review and also I'd like to  
9 thank the nonclinical review team in FDA for all their  
10 work and lastly, I want to introduce Dr. Sherri  
11 Berman, the clinical reviewer.

12 DR. BERMAN: Okay, good morning. I'm  
13 Sherri Berman, an ophthalmologist and I was the  
14 clinical reviewer for this PMA. First of all, I'd  
15 like to thank Refractec for their cooperation in  
16 providing us here at FDA in advance with their Panel  
17 presentation. I have for you today six questions for  
18 the Panel to consider as part of their discussion  
19 today and rather than reiterate what has already been  
20 presented by Refractec I have put together myself a  
21 few summary tables that I feel are relevant to each of  
22 these questions and I'd like to just go through them  
23 briefly right now.

24 The first question that the Panel will be  
25 asked is for their concerns regarding the incidents of

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1 induced cylinder with significant axis shift and its  
2 consequent effect on efficacy.

3 As part of the surgical procedure with  
4 this device, the positioning and angle of the  
5 handpiece as it enters the cornea as well as the  
6 centration on the pupil are performed manually by the  
7 surgeon. I've put together this slide to summarize  
8 the difference between pre-op and post-op cylinder  
9 magnitudes. I'll give you a minute to look it over  
10 and as you can see here, for the more than or equal to  
11 1.00 diopter and the greater than 1.00 diopter  
12 stratifications, the incidence of induced cylinder was  
13 20 to 30 percent at month 1 and declined over time,  
14 but at month 9 and month 12 still a significant  
15 proportion of eyes have this level of induced  
16 cylinder.

17 Here you can see a summary of the change  
18 in the vector magnitude and again, there's a  
19 significant proportion of eyes that had more than or  
20 equal to 1.00 diopter of induced change.

21 In this table, you can see that  
22 approximately 40 to 50 percent of eyes had a shift in  
23 cylinder axis of more than 30 degrees and  
24 approximately 25 percent had an outcome shift of  
25 greater than 60 degrees. The direction of the final

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1 post-op axis appears to be somewhat unpredictable and  
2 widely variable.

3 In this slide of post-op cylinder  
4 magnitude, I first want to point out that all eyes as  
5 an entry criteria had a baseline cylinder magnitude of  
6 three quarters of a diopter or less. It is of  
7 clinical significance that the magnitude of post-op  
8 residual cylinder of greater than or equal to 1.00  
9 diopter was 40 percent of eyes at month 6 and 32  
10 percent of eyes at month 12.

11 Finally, with respect to this first  
12 question for the Panel, in order to further assess the  
13 clinical significance of induced cylinder, an analysis  
14 was requested by FDA of the sponsor and was performed  
15 as such.

16 I want to clarify that the percentages  
17 that I've put together in this table differ very  
18 slightly from those presented in the Panel  
19 presentation by Refractec because they presented data  
20 on the -- I believe 21 eyes from the current nomogram  
21 treatment, whereas these numbers represent the total  
22 25 eyes that were treated, but the percentages did not  
23 differ by more than a few percentages and here the  
24 stratification is eyes with less than a diopter of  
25 induced cylinder at 12 months and eyes with more than

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1 or equal to a diopter of cylinder and you can see that  
2 almost double the proportion of eyes achieved 20/20  
3 with less than a diopter cylinder and significant  
4 differences at 20/25 level and the 20/40 level,  
5 although not as significant as the difference at the  
6 20/20 level.

7 And as well, was presented the mean  
8 uncorrected visual acuity which I don't think gives  
9 the whole picture.

10 The second Panel question is as follows:  
11 Is 12-month follow-up sufficient to provide reasonable  
12 assurance of safety and efficacy? There are 21 eyes  
13 available at 20 months. Should data for these eyes be  
14 required in the labeling?

15 In addition, the third question, does the  
16 refractive correction obtained with this device in  
17 light of the rate of change of mean MRSE over time and  
18 the incidence of over and under-correction justify  
19 potential risks.

20 For example, from one of the sponsors PMA  
21 analyses, it was presented that only 32 percent of the  
22 363 eyes in the efficacy cohort achieved a final UCVA  
23 greater than or equal to their baseline BCVA.

24 The stability data was presented earlier  
25 and I won't focus on this for too long, but I do just

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1 want to point out some numbers because they are  
2 pertinent to the requested indication statements and  
3 that is when you look at the mean change over time and  
4 the extrapolated annual change, I just want to point  
5 out that over the 6 to 9 month interval and the 9 to  
6 12 month interval and the 12 month consistent cohort  
7 that there certainly is no demonstration of the fact  
8 that the rate of refractive regression is slowing  
9 down. And this is confirmed with the larger cohort  
10 with two consecutive visits.

11 Further data to look at for these two  
12 questions for the Panel, focus on accuracy of the MRSE  
13 and here you can see that the rate of undercorrection  
14 was as follows here and when the sponsor stratified  
15 this data by the degree of pre-op hyperopia there was  
16 a suggestion of a trend of decreasing efficacy with  
17 increasing pre-op CRSE.

18 Here you can also see that a significant  
19 percentage of eyes developed early clinically  
20 significant myopia, the incidence of which declined  
21 dramatically over time. These patients were like to  
22 require spectacle or contact lens correction at least  
23 part-time. Overall, these outcomes are consistent  
24 with the post-operative hyperopic shift over time.

25 The fourth question that the Panel will be

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1 asked to consider is as follows: Are there concerns  
2 regarding the increased incidence of visual symptoms  
3 from pre-op levels?

4 As this was also presented extensively by  
5 the sponsor, I won't deliberate here, but you can look  
6 over these numbers and I also want to point out that  
7 in addition to the moderate and severe symptoms  
8 reported, it was also clinically interesting that the  
9 proportion of eyes that reported none for each of  
10 these symptoms decreased over time for many of the  
11 symptoms including halos, diplopia, visual fluctuation  
12 and night driving problems so that eyes did not have  
13 any symptoms pre-operatively did develop symptoms  
14 post-operatively.

15 In addition, the subjective assessment of  
16 overall satisfaction revealed that a rating of  
17 dissatisfied or very dissatisfied was reported by 8  
18 percent of subjects at month 6 and 12 percent of  
19 subjects at month 12.

20 The fifth question: Do the safety and  
21 efficacy data presented in this PMA support approval  
22 of this device for the requested indication? Is the  
23 requested indication appropriate as worded, based on  
24 the study outcome?

25 I prepared these slides and they were

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1 accurate up until about a week ago. The sponsor had  
2 modified somewhat the requested indication down in  
3 this area so I'm apologizing that it's not 100 percent  
4 accurate, but I've highlighted in yellow the areas of  
5 the requested indication statement that I'd like the  
6 Panel to address during their deliberations.

7 And these basically are the upper limit of  
8 the cycloplegic spherical equivalent and the wording  
9 or such of the statement that the magnitude of  
10 correction decreases over time and how much it does  
11 so.

12 In one of the amendments to the PMA,  
13 Refractec provided an additional analysis in response  
14 to one of the primary Panel reviews which is  
15 summarized here. In this amendment, they concluded a  
16 highly significant correlation between baseline CRSE  
17 and induced cylinder. Most pronounced in eyes with a  
18 baseline CRSE more than 2.50 diopters. Due to the  
19 small sample size of the eyes with treatment size of  
20 eight spots, these numbers cannot be used to make  
21 statistically valid conclusions. The sponsor proposed  
22 that these outcomes be addressed by them in the device  
23 labeling or alternatively by modification of the upper  
24 limit of the refractive range.

25 At this time I have no further clinical

1 data to present.

2 Okay, the final question for Panel  
3 consideration is a general question, what are your  
4 recommendations for labeling regarding regression of  
5 effect, induction of cylinder and incidence of visual  
6 symptoms? Are there any additional labeling  
7 recommendations?

8 DR. SUGAR: Thank you. Are there  
9 questions for Dr. Berman or for the Agency?

10 If not, I'd like to -- go ahead, I'm  
11 sorry.

12 DR. BRADLEY: Arthur Bradley. You were  
13 apologizing for one item on that segment from last  
14 slide being out of date.

15 Would you mention what has changed?

16 DR. BERMAN: Yes. At the time that I  
17 prepared these slides, the requested indication for  
18 use from the sponsor, the final bullet here they  
19 requested was the statement that the magnitude of  
20 correction diminishes over time with an average loss  
21 of approximately 10 percent of the intended correction  
22 at one year.

23 I would have to defer to sponsor --

24 DR. SUGAR: It would be slide 85 from the  
25 sponsor's package you have in front of you, where they

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1 changed that to 6 percent of the intended correction  
2 at one year and they added the statement the  
3 proportion of intended correction retained beyond 12  
4 months is undetermined.

5 If there are no other questions for the  
6 Agency, the sponsor will have additional time right  
7 after lunch, whether that means we'll be better able  
8 to attend or less, I'm not sure, but I would like to  
9 have everybody really get back here at 1 o'clock so  
10 that we can proceed to pace.

11 (Whereupon, at 12:01 p.m., the meeting was  
12 recessed, to reconvene at 1:00 p.m.)

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