

FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
OPHTHALMIC DEVICES PANEL
Eighty-Seventh Meeting

Tuesday,
January 14, 1997

Grand Ballroom
Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

IN ATTENDANCE:

Voting Panel Members

C. PAT WILKINSON, M.D., Interim Chair
MARK A. BULLIMORE, Ph.D.
EVE J. HIGGINBOTHAM, M.D.
MARK J. MANNIS, M.D., Consultant, deputized to vote
JAMES P. McCULLEY, M.D.
RICHARD S. RUIZ, M.D.
P. SARITA SONI, O.D.
WOODFORD S. VAN METER, M.D., Consultant, deputized to vote

Non-Voting Panel Members

FREDERICK FERRIS, M.D., Liaison, National Eye Institute
JUDY F. GORDON, D.V.M., Industry Representative
ELEANOR McCLELLAND, Ph.D., Consumer Representative

Food and Drug Administration Participants

SARA M. THORNTON, Panel Executive Secretary

C O N T E N T S

PAGE

Call to Order

C. Pat Wilkinson, M.D., Interim Chair 4

Introductory Remarks, Welcome to New Panel
Members, and Introduction of Panel Members

Sara M. Thornton, Executive Secretary 4

Conflict of Interest Statement and
Appointment to Temporary Voting Status

Sara M. Thornton, Executive Secretary 7

CONSIDERATION OF PMA P930016/S3

Introduction by FDA Staff

Morris Waxler, Ph.D.
Acting Chief
Diagnostic and Surgical Devices Branch 11

Jan C. Callaway, PMA Team Leader 12

PMA Sponsor Presentation 15

FDA Clinical Review

Malvina B. Eydelman, M.D.
Medical Officer
Division of Ophthalmic Devices 49

Primary Panel Reviews

Woodford S. Van Meter, M.D. 61

James P. McCulley, M.D. 65

Panel Discussion

75

P R O C E E D I N G S (9:05 a.m.)

1
2 DR. WILKINSON: Good morning. I'd like to
3 welcome each of you to the second day of the 87th session
4 of the Ophthalmic Devices Panel. I'll turn over the
5 microphone to Ms. Thornton for some introductory remarks.

6 MS. THORNTON: Good morning and welcome to all
7 attendees. Before we proceed today with the panel
8 introductions, I just wanted to note, as I did in the
9 record yesterday but for those who are here today for the
10 first time, that since our last meeting in July of 1996
11 we've made a few changes to the panel.

12 A voting member, Dr. Alexander Brucker, his
13 term as a voting member has been completed and he is now a
14 member of our consultant group and no longer a voting
15 member. Dr. Richard Abbott, a voting member, had to retire
16 from his term and he is now with us as a consultant. We're
17 fortunate to still have these folks with us for advice and
18 counsel and consulting.

19 I would like to now introduce the three new
20 voting members who we are welcoming today to the panel.

21 Dr. James McCulley is Professor and Chairman of the
22 Department of Ophthalmology at the University of Texas
23 Southwestern Medical School in Dallas, Texas. Dr.

24 ~~McCulley's area of expertise is corneal and external~~

1 disease and refractive surgery. Dr. Eve Higginbotham is a
2 specialist in the treatment of glaucoma and is Professor
3 and Chair of the Department of Ophthalmology at the
4 University of Maryland School of Medicine in Baltimore,
5 Maryland. Dr. Mark Bullimore, a noted vision scientist, is
6 an Assistant Professor, College of Optometry at Ohio State
7 University.

8 I'd like to welcome them all as new voting
9 members.

10 I would also like to take this time to
11 introduce a new consultant member to our group, Dr. Mark
12 Mannis. Dr. Mannis, an internationally recognized expert
13 on corneal and refractive surgery, is Professor of
14 Ophthalmology and Director of the Corneal and External
15 Disease and Refractive Surgery Service at the University of
16 California Davis School of Medicine.

17 Welcome, Dr. Mannis.

18 Would the remaining panel members please
19 introduce themselves to the public and staff? I'd like to
20 begin with Dr. Judy Gordon.

21 DR. GORDON: Dr. Judy Gordon, Vice President of
22 Scientific Affairs at Chiron Vision, and I'm the industry
23 representative to this panel.

24 ~~DR. McCLELLAND: Eleanor McClelland, Associate~~

1 Dean for Undergraduate Studies and Community Affairs,
2 University of Iowa College of Nursing, and a consumer
3 member on the panel.

4 DR. SONI: Sarita Soni. I'm a Professor of
5 Optometry and Vision Science and Associate Dean for
6 Research in the graduate program at Indiana University.

7 DR. RUIZ: Richard Ruiz, Chairman of the
8 Department of Ophthalmology, University of Texas, Houston.

9 DR. WILKINSON: I'm Pat Wilkinson, Chairman of
10 the Department of Ophthalmology at Greater Baltimore
11 Medical Center, and Professor of Ophthalmology at Johns
12 Hopkins.

13 DR. VAN METER: Woody Van Meter. I'm in
14 private practice in corneal and external disease in
15 Lexington, Kentucky.

16 DR. ROSENTHAL: I'm Ralph Rosenthal, Director,
17 Division of Ophthalmic Devices, FDA.

18 MS. THORNTON: Thank you, everyone.

19 I just wanted to make a couple of
20 announcements. During the break there will be a snack bar
21 set up outside the room for the public and FDA staff. At
22 the lunch break following the open session there is
23 reserved seating for the panel at the Village Park Cafe
24 just outside this room, down to your left.

1 Also, I'd like to announce for the record that
2 this meeting is scheduled to adjourn at 5:00 p.m. today.
3 The meeting will have to end at 6:00 p.m. as another group
4 has retained the meeting room after 6:00. This could
5 happen.

6 Now I'd like to move on to open the open public
7 hearing session. Any speakers who wish to make a
8 presentation before the committee are doing so in response
9 to the panel meeting announcement in the Federal Register.
10 They're not specifically invited to speak by FDA, nor are
11 their comments data or products endorsed by the agency.

12 There are no scheduled speakers today.
13 However, Dr. Wilkinson will recognize unscheduled speakers
14 during the open public hearing time. After a speaker has
15 completed his or her remarks, the Chair may ask them to
16 remain if the committee wishes to question them further.
17 Only the Chair and members of the panel may question
18 speakers during the open public hearing.

19 DR. WILKINSON: Any unscheduled speakers out
20 there that would like to present their story to the panel?

21 (No response.)

22 DR. WILKINSON: I don't see any takers, so
23 we'll move on. This will officially terminate the open
24 public session.

1 We'll now open the committee discussion. Ms.
2 Thornton will make several remarks for the record at this
3 time.

4 MS. THORNTON: The following announcement
5 addresses conflict of interest issues associated with this
6 meeting and is made part of the record to preclude even the
7 appearance of an impropriety.

8 To determine if any conflict existed, the
9 agency reviewed the submitted agenda and all financial
10 interests reported by the committee participants. The
11 conflict of interest statutes prohibit special government
12 employees from participating in matters that could affect
13 their or their employer's financial interest. However, the
14 agency has determined that participation of certain members
15 and consultants, the need for whose services outweigh the
16 potential conflict of interest involved, is in the best
17 interests of the government.

18 Full waivers have been granted to Drs. James
19 McCulley and Woodford Van Meter for their interest in firms
20 at issue that could potentially be affected by the
21 committee's deliberations. Copies of these waivers may be
22 obtained from the agency's Freedom of Information Office,
23 Room 12A-15 of the Parklawn Building.

24 We would like to note for the record that the

1 agency took into consideration a certain matter regarding
2 Dr. Mark Bullimore. Dr. Bullimore reported that he was a
3 consultant on a one-day study for which a firm at issue
4 donated money to his university. Since this is a past
5 involvement and unrelated to the issue before the panel,
6 the agency has determined that he may participate fully in
7 today's deliberations.

8 In the event that the discussions involve any
9 other products or firms not already on the agenda for which
10 an FDA participant has a financial interest, the
11 participant should exclude themselves from such
12 involvement, and their exclusion will be noted for the
13 record.

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

19 Thank you.

20 Now I'd like to read into the record the
21 appointment to temporary voting status.

22 "Pursuant to the authority granted under the
23 Medical Devices Advisory Committee Charter, dated October
24 27, 1990, as amended October 20, 1995, I appoint the

1 following individuals as voting members of the Ophthalmic
2 Devices Panel for the duration of this meeting on January
3 14, 1997: Dr. C. Pat Wilkinson, Dr. Woodford S. Van Meter,
4 Dr. Mark J. Mannis. For the record, these persons are
5 special government employees and are consultants to this
6 panel or consultants or voting members of another panel
7 under the Medical Devices Advisory Committee. They have
8 undergone the customary conflict of interest review and
9 have reviewed the material to be considered at this
10 meeting."

11 Signed, D. Bruce Burlington, M.D., Director,
12 Center for Devices and Radiological Health, December 16,
13 1996.

14 Thank you, Dr. Wilkinson.

15 DR. WILKINSON: It's my understanding we now,
16 as we move into the introduction of the PMA, will hear some
17 statements by Dr. Waxler regarding an update related to
18 refractive surgery.

19 DR. WAXLER: Good morning. First an interim
20 report on reimported and unique lasers. January 15th is
21 the deadline for submitting to FDA self-certification for
22 reimported lasers and for IDEs for these lasers, and for
23 unique lasers. Self-certifications have been submitted by
24 10 owners of reimported lasers. Eight of these

1 certifications have been determined to be inadequate, and
2 IDE submissions have been requested. Two self-
3 certifications require additional information to be
4 submitted to FDA for determination of adequacy. Three IDE
5 applications have been submitted for unique lasers.

6 Because of the guidance for refractive surgery
7 lasers and the training which has been provided on this
8 guidance, we have set a 10-day goal for review of lasers
9 for refractive surgery, for IDEs for these kinds of
10 products. The statutory review time remains 30 days.

11 We conducted two one-day training sessions on
12 the guidance for refractive surgery lasers; 35 individuals
13 attended the training.

14 A point to take note, manufacturers may not
15 distribute lasers without their own IDE submitted to the
16 agency. Sponsor investigators who submit an IDE for
17 studies at a manufacturer's investigational site should
18 provide a scientific rationale for the study which is
19 distinctive from the studies being conducted by the
20 manufacturer, obtain a letter of reference from the
21 manufacturer and letters describing mutual agreement that
22 the data will be provided to the manufacturer in support of
23 a PMA.

24 ~~Several suggestions have been submitted for~~

1 changes in the guidance for refractive laser surgery. We
2 are reviewing these ideas. We would appreciate your views
3 on these issues at another meeting of the panel.

4 DR. WILKINSON: Thank you. We will now move
5 forward and introduce this PMA, please.

6 DR. WAXLER: The agency brings this supplement
7 to PMA application P930016 before this panel under two
8 contrasting sets of expectations: go faster, but be
9 cautious. Take into account the practical realities of
10 correction of astigmatism given current approval of this
11 device only for myopia without astigmatism, but base
12 decisions on rigorous clinical trial data. Utilize the
13 guidance on refractive surgery lasers, but be aware that
14 this guidance is not complete with regard to expected
15 clinical outcomes for treating astigmatism. Provide the
16 panel with FDA's independent analysis of the data, but do
17 not lead the panel toward a particular decision. Follow
18 FDA regulations which define reasonable assurance of safety
19 and effectiveness to include a wide variety of data,
20 including case studies as well as randomized controlled
21 clinical trials, but emphasize controlled clinical trial
22 data in making decisions.

23 We attempted to balance these conflicting sets
24 of expectations in reviewing and presenting this

1 application. We seek your best clinical and scientific
2 advice on this PMA supplement.

3 Jan Callaway is the team leader for this
4 application. After Ms. Callaway presents her remarks,
5 representatives of VISX will make their presentation, and
6 then Dr. Malvina Eydelman will provide her independent
7 analysis of the data.

8 Jan?

9 MS. CALLAWAY: Good morning. I'm Jan Callaway,
10 the team leader for the VISX astigmatism PMA supplement.

11 On March 27th, 1996, in PMA application
12 P930016, VISX, Inc., of Santa Clara, California, received
13 approval for its argon fluoride excimer laser. The device,
14 the VISX excimer laser system models B and C, is intended
15 for use in photorefractive keratectomy to correct low to
16 moderate myopia up to 6 diopters. This PMA supplement was
17 filed on August 26th, 1996, requesting approval for a new
18 indication for use to treat patients with not less than
19 0.75 diopters and not more than 4 diopters of astigmatism.

20 Because no legally marketed device is available
21 for the safe treatment of astigmatism along with
22 photorefractive keratectomy for myopia, and the alternative
23 treatments being employed entail substantial risk of
24 morbidity for the patient, FDA also granted this PMA

1 supplement expedited review status. The clinical study was
2 conducted under Investigational Device Exemption G910064,
3 which was approved on June 7, 1991.

4 The VISX excimer laser system used for
5 correction of astigmatic refractive error is the same
6 system approved and used for the correction of simple mild
7 to moderate myopia, producing pulses at 193 nanometer
8 wavelength, with a fluence per pulse of 160 millijoules per
9 centimeter squared, and an ablation depth per pulse of
10 approximately one-quarter micron. The pulse duration is 20
11 nanoseconds, with a repetition rate of 5 hertz.

12 The primary panel reviewers for this
13 application are Dr. James McCulley and Dr. Woodford Van
14 Meter. Panel input is required in this area because
15 clinical judgment is required to evaluate the data. Your
16 comments from the discussion today will help us in
17 evaluating the safety and efficacy of the device for this
18 indication for use.

19 The review team evaluating the PMA supplement
20 included the following reviewers: for engineering and
21 labeling found in the operator's manuals, Dr. Morwood
22 Ediger; for patient information labeling, Ms. Carol
23 Clayton; statistical reviews were done by Mr. Mel Sideman
24 and Mr. F.C. Lu; the vision and engineering physics reviews

1 were done by Dr. Bruce Drum; and the clinical review was
2 done by Dr. Malvina Eydelman.

3 I would like to thank these team members for
4 the outstanding job they did in expediting the review of
5 this document.

6 The sponsor will make their presentation of the
7 PMA at this time, followed by Dr. Eydelman's discussion of
8 her review.

9 At this time I would like to introduce Mr. Dave
10 Patino, Vice President of Regulatory and Clinical Affairs,
11 VISX, Inc.

12 DR. WILKINSON: You will note this represents a
13 change in order from what used to be the standard. But as
14 far as I know, from this time forward the sponsors will be
15 expected to present their data first since they generated
16 the data, and this will now be followed by the agency
17 reviewer, who will hopefully not simply review what's been
18 reviewed once but will make comments upon the review of the
19 data, and then we'll proceed to a panel discussion.

20 MR. PATINO: Good morning, members of the FDA
21 and the panel, ladies and gentlemen. I am Dave Patino,
22 Vice President of Regulatory and Clinical Affairs at VISX.
23 Going back to the Ophthalmic Devices Panel meeting of last
24 July, there was much discussion, and I would say hotly

1 debated, relating to the issues including the practice of
2 medicine, which resulted in a discussion between the panel
3 and the FDA relating to the types of data that would be
4 appropriate to present to the panel for consideration in
5 order to expand the indications for laser vision
6 correction.

7 As we are all keenly aware, presently the
8 community, in order to address off-label use such as
9 astigmatism, can employ the use of multiple procedures such
10 as the sequential use of PTK and PRK with and without
11 incisional techniques, all of which the safety and efficacy
12 are unknown. The July panel discussion focused on the
13 extent of data needed for the expansion of indications for
14 those laser manufacturers who are already approved by the
15 Food and Drug Administration. The July panel discussions
16 focused on what I will call a rather untraditional approach
17 as compared to the rigor of the more traditional FDA
18 approach for the numbers of subjects and follow-up time for
19 expansion of indications.

20 The discussions centered on FDA-approved
21 lasers, and when the requested new indication did not
22 represent any new safety concerns, the resulting clinical
23 trial data would therefore focus on efficacy. An example
24 that was mentioned frequently was astigmatism. In part,

1 the July panel discussions reached a consensus on, one, the
2 acceptance of internationally peer-reviewed literature
3 articles, along with smaller numbers of patients involved
4 than in the past; two, the patients have consented to the
5 study either with a typical informed consent form or in
6 conformance to the Declaration of Helsinki; and three, the
7 follow-up time of six months would be acceptable.

8 I will now show the conclusion of the July
9 panel discussions relating to this topic.

10 (Videotape presentation.)

11 MR. PATINO: VISX attended the July panel
12 meeting and listened to these discussions. We then
13 reviewed our current, ongoing clinical trials to determine
14 the most appropriate candidate for submission. We believe
15 that the data that we have submitted for our astigmatism
16 indication constitutes valid scientific evidence and is
17 consistent with the July panel discussion since, one, our
18 international clinical data is far superior to peer-
19 reviewed publications since more details of the actual data
20 are available to us compared simply to a literature article
21 -- our international data that we used to substantiate our
22 U.S. clinical trials are from Moorfields in the U.K. and
23 from the University of Ottawa Eye Institute, Ottawa,
24 Canada; two, these international clinical trials were

1 subject to informed consent, ethical review boards, and are
2 consistent with the Declaration of Helsinki; three, our
3 follow-up time of up to two years greatly exceeds the six
4 months, as discussed during the July panel meeting; and
5 four, the VISX clinical data for astigmatism present no new
6 safety issues, and the outcomes are consistent with our
7 approved PRK indication.

8 We thank you for your consideration.

9 I will now turn our presentation over to Dr.
10 Marc Odrich, Assistant Professor of Ophthalmology and
11 Director of Refractive Surgery at Columbia University, who
12 is the medical monitor for VISX.

13 Dr. Odrich.

14 DR. ODRICH: Thank you, David.

15 Good morning. VISX is asking for --

16 DR. WILKINSON: Excuse me. We need for the
17 record for you to state your financial involvement with the
18 company.

19 DR. ODRICH: Sure. I am Dr. Marc Odrich. I am
20 a paid medical monitor for VISX, Inc., and a paid
21 consultant to the company.

22 DR. WILKINSON: Thank you.

23 DR. ODRICH: Thank you.

24 ~~VISX is asking for photorefractive keratectomy~~

1 for astigmatism, for the indications of zero to 6 diopters
2 of spherical myopia at the spectacle plane, with
3 concomitant astigmatism of -0.75 to 4 diopters of
4 astigmatism also at the spectacle plane. The device is
5 identical to the approved device in the United States
6 currently. Specifically, please note that the wavelength
7 is the same, the repetition rate as approved in the United
8 States is the same, the fluence, the beam and calibrations
9 are identical.

10 The number of eyes treated in three monitored,
11 peer-reviewed clinical trials is 741 eyes, 643 of which
12 were seen and the results analyzed at 12 months or longer.
13 The breakdown is listed on the slide for you. There are
14 116 treated U.S. eyes that were analyzed. The University
15 of Ottawa contributed 95 of these eyes. There are 530 eyes
16 from Moorfields.

17 The VISX excimer laser system is approved to
18 treat low to moderate degrees of myopia using a circular
19 beam. To correct for myopic astigmatism, the identical
20 VISX excimer laser system can be and is internationally
21 used with a radial asymmetric beam, with no increase in
22 maximal depth of ablation.

23 Dr. Bruce Jackson has been the principal
24 investigator for the University of Ottawa clinical trial,

1 and this has been a prospective sequential study consistent
2 with informed consent, with the Declaration of Helsinki,
3 and an ethics review board that requires bi-yearly
4 presentation. The Moorfields clinical trials, with the
5 principal investigator being Dr. Julian Stevens, has been a
6 parallel study with prospective, sequential patient
7 treatment and Declaration of Helsinki and ethics review
8 board compliance.

9 The United States study is a multicenter, five
10 clinical site prospective study with consents conforming to
11 IDE and IRB requirements. The five institutions are
12 Catholic Medical Center, Dohini Eye Institute of the
13 University of South California, the Executive Park Surgery
14 Charles Cosine, Sinai Hospital, and the University of South
15 Florida.

16 The VISX IDE called for 133 eyes to be treated
17 with a spherical equivalent, and of these eyes, 116
18 fulfilled our indications. These indications are zero to 6
19 diopters of spherical myopia with a concomitant astigmatism
20 of -0.75 to 4 diopters of cylinder. There were 71 primary
21 eyes, 45 fellow eyes, and these were assessed for
22 poolability by making sure that all preoperative
23 demographic characteristics had no statistically
24 significant differences.

1 Finally, our accountability for the 116 eyes
2 shows that at the final visit, which is at 20 months or
3 longer, had 92.3 patients.

4 I will now ask Dr. Julian Stevens to come
5 forward. Dr. Stevens is a consultant ophthalmologist at
6 Moorfields Eye Hospital, the principal investigator for the
7 study at Moorfields, and will present the effectiveness
8 data of the United States cohort first.

9 Dr. Stevens?

10 DR. STEVENS: Thank you very much, Dr. Odrich.

11 My name is Julian Stevens, and I --

12 DR. WILKINSON: Dr. Stevens, excuse me. Again,
13 for the record, let us know about your financial
14 involvement.

15 DR. STEVENS: I'm consultant ophthalmologist at
16 Moorfields Eye Hospital. My expenses to travel here today
17 have been funded by VISX, as approved by my hospital
18 research and ethics committee. The research study that
19 will be presented from Moorfields is independent of VISX.
20 There are no financial arrangements.

21 The U.S. data that we're going to present is
22 for the treatment of up to -6 diopters of spherical myopia
23 at the spectacle plane, with the addition of 0.75 to 4
24 diopters of astigmatism at the spectacle plane.

1 The history of astigmatism is that Isaac Newton
2 wrote about it in his Principia Optica when he described
3 the optical principles of astigmatism in the 1600s, and
4 that's because he had astigmatism himself. Donders first
5 described ocular astigmatism and its theoretical correction
6 in the 1800s, and Thomas Airy in Cambridge developed the
7 first sphericylindrical lens since he was an astronomer and
8 he needed the best possible optics for his work.

9 We've now had astigmatic spectacle correction
10 available commercially for about 100 years. The natural
11 history of astigmatism is that at birth there is normally
12 little or no astigmatism, but within only a few months a
13 small amount of natural astigmatism develops as the eye
14 grows. By adulthood, only 14 percent of eyes have no
15 recordable refractable astigmatism, and 27 percent have one
16 or more diopters of astigmatism, and 9 percent two or more
17 diopters.

18 One of the problems with this is that there's
19 no single-point focus, neither for distance or near and the
20 reduced uncorrected vision. It is sometimes difficult to
21 be precise or accurate in terms of optical correction.
22 Each method has its disadvantages. Spectacle correction is
23 associated with meridional and other distortions as a
24 magnification effect, and this causes an image tilt. Soft

1 toric contact lenses may also be problematic since even a
2 small degree of rotation of the lens causes itself an
3 induced astigmatism.

4 For very high astigmatism, rigid gas permeable
5 toric lenses are often the preferred option of optical
6 correction.

7 What I've done here is I've taken at the top
8 some blocked capital letters and applied an astigmatic
9 blur, increasing as you go down. On the lefthand side it's
10 a vertical blur, and on the righthand side it's a
11 horizontal blur. You can see the effect of astigmatism in
12 different meridians. It is different. Text is very
13 difficult with a horizontal blur.

14 We've been able to correct astigmatism, or at
15 least attempt to, for at least a century, since it was well
16 known from the early cataract surgery that the incisions
17 induced astigmatism, and nowadays we reduce or even induce
18 astigmatism, often with variable results, during incisional
19 surgery.

20 The excimer laser system is a new device which
21 can be used to treat astigmatism, and in particular the
22 VISX excimer laser system, which is already approved to
23 treat low to moderate degrees of myopia using a circular
24 beam, the identical system can be applied using a radial

1 asymmetric beam without an increase in the maximal depth of
2 central ablation. The indication sought, up to 6 diopters
3 of myopia and up to 4 diopters of astigmatism at the
4 spectacle plane, doesn't result in an overall deeper
5 ablation than the currently approved low to moderate PRK
6 indications.

7 How does the laser actually achieve its effect?

8 You can see that on the blue principal meridian there's
9 relatively less curvature than in the red short principal
10 meridian. So you can see that this differential curvature
11 is able to treat a differential power across the cornea.
12 The blue meridian treats the sphere, and the red meridian
13 treats the sphere plus the astigmatism.

14 The machine itself achieves this by a
15 relatively simple mechanism. There's the central circular
16 expanding diaphragm which is used to treat myopia, but in
17 addition there are two parallel blades which can be rotated
18 completely through 360 degrees, and the combination of
19 these parallel blades plus the circular aperture generates
20 the toric effect that you saw in the previous slide.

21 When we actually look at excimer laser
22 treatments, what patients are after is uncorrected visual
23 acuity, so that in itself is the first outcome measure. We
24 need to assess process, what we've actually achieved, and

1 to do that we need to look at vector analysis, the induced
2 vector change. In terms of further analysis of outcome, we
3 need to look at the scalar astigmatism, the amount that
4 we've actually achieved in terms of its reduction.

5 This slide is of the U.S. multicenter data, and
6 it comprises 71 primary eyes and 45 fellow eyes. This
7 slide shows that there's no difference in any pretreatment
8 parameter between the primary and the fellow eyes.

9 This slide summarizes the uncorrected visual
10 acuity, 20/30 or better. No patient before treatment
11 achieved this level of uncorrected acuity, but 78.6 percent
12 achieved this level at the final visit. Taking 20/40 or
13 better, again no patient had this level of acuity before
14 treatment, but 88.1 percent achieved this at the final
15 visit.

16 How do we actually assess astigmatism in terms
17 of its process? Here, after all, the vector is on a simple
18 diagram. We have to use vector analysis to assess process
19 because astigmatism has both magnitude and direction. We
20 can't have a single number to express these two components.
21 So what we have to do is measure the effect of the surgical
22 treatment to know the intended change of magnitude and
23 axis, and assess the vector-achieved change. Knowing this,
24 we can also assess the intended undercorrections of both

1 cylinder and sphere for our analysis.

2 If we overcorrect astigmatism, what we see is a
3 very large axis shift or axis flip. A small
4 undercorrection tends to result in much greater axis
5 stability in any residual astigmatism, which effectively is
6 a comfort zone for the patient.

7 Each eye for the U.S. study and for the
8 international data was assessed at 6 months, 12 months, and
9 at the final visit. The intended versus the achieved
10 magnitude was assessed, and the intended versus achieved
11 axis or axis error was also assessed. All individual
12 assessments were then analyzed in a batch at each time gate
13 to allow the mean or standard deviation characterization in
14 a standard statistical manner.

15 This slide shows the vector analysis of the
16 cohort at the final visit. If we look at the top line, the
17 mean, the mean sphere before treatment was -3.52 diopters,
18 and the mean astigmatism was -1.64. At the final visit the
19 mean sphere was -0.1 diopters, and the mean cylinder was
20 -0.55. If we go to the righthand side of the slide, at the
21 intended refractive change, looking at the astigmatism, the
22 intended change was 1.44 diopters, and the achieved change
23 in the SIRC column was 1.14.

24 ~~If we now look at a vector analysis of the~~

1 cohort stratified -- and this is a key slide because it
2 does show how small, moderate, and high degrees of
3 astigmatism behave in terms of their treatment and outcome.
4 If we look at the preoperative astigmatism of 0.75 to 1
5 diopter, relatively low, we see that the intended change
6 was 1.3 diopters, and the achieved change -- I mean, I
7 can't even see this from here, so I don't know how you can
8 either. We'll go to the next slide actually. That data is
9 all submitted in the written data beforehand.

10 What we're going to go to now is the vector
11 error in terms of the axis error. The mean axis error was
12 11.5 degrees, and the mean magnitude error was very small,
13 -0.3 diopters. The cylinder reduction -- this is the
14 scalar reduction that I mentioned earlier -- the mean
15 pretreatment astigmatism was -1.64 diopters, and at six
16 months was -0.49 diopters, at 12 months -0.51, and at the
17 final visit 0.55. If we look at six months to the final
18 visit, there was no statistically significant change
19 between this gate. In other words, the patients became
20 stable at this six-month time gate.

21 Astigmatism itself was reduced. At six months
22 it was reduced by 70 percent, and at 12 months a mean of 66
23 percent, and at the final visit a mean of 64 percent in
24 this U.S. data set.

1 So in summary, 88.1 percent of patients
2 achieved an uncorrected visual acuity of 20/40 or better.
3 There was a mean 64 percent reduction in the magnitude of
4 the astigmatism as a scalar quantity when assessed at the
5 last visit, and there was no statistically significant
6 difference between the magnitude of astigmatism at 6
7 months, 12 months, and at the final visit. A full vector
8 analysis demonstrated that a small absolute vector axis
9 change was present, and a small magnitude undercorrection.

10 Thank you very much.

11 DR. ODRICH: Thank you, Dr. Stevens.

12 I'd like to ask Dr. James Salz, Clinical
13 Professor of Ophthalmology at the University of Southern
14 California and a paid consultant to VISX, to come forward
15 to discuss the safety summary of the PRK trial.

16 Dr. Salz?

17 DR. SALZ: Thank you, Marc, and good morning.
18 Although I haven't been paid yet, I hope I am a paid
19 consultant to VISX.

20 (Laughter.)

21 DR. SALZ: In preparing for this meeting and
22 looking at the data, I was impressed that the low incidence
23 of complications that we found in this PRKa study was quite
24 similar to the results that we presented for low to

1 moderate myopia. Intuitively one would expect that since
2 we're using the same laser system and we're not performing
3 ablations that were any deeper at its maximum than in the
4 spherical myopia study.

5 One of the most important safety parameters is
6 the incidence of potentially sight-threatening
7 complications, and in this study we had no hypopia, no
8 corneal perforation, no endophthalmitis, no corneal
9 decompensation. There was, however, one corneal
10 infiltrate, and I'd like to discuss that case in detail.

11 This was a patient who had a soft contact lens
12 discontinued at day three, developed a corneal infiltrate
13 at day seven. The surgeon elected not to culture that
14 infiltrate, so we don't have a positive culture. It was
15 suspected to be bacterial. It was treated with intense
16 topical antibiotics. The preoperative best spectacle
17 corrected visual acuity in that eye was 20/20. At its very
18 worst, which was six months post-treatment, it was reduced
19 to 20/30, and then recovered to 20/25 by 12 months, and
20 back to 20/20 by the final visit, and had an uncorrected
21 acuity of 20/40.

22 Lens opacities were also noticed in this study,
23 and the Beaver Dam definition of a lens opacity is one that
24 does not reduce the vision worse than 20/30. In a cataract

1 it's if it does reduce best spectacle corrected visual
2 acuity greater than 20/30. There were two patients,
3 including three eyes, that had lens opacities graded on
4 entry into the study, and there was one patient where both
5 eyes developed nuclear sclerotic and posterior subcapsular
6 cataracts, and this patient was age 71 on entry into the
7 study.

8 Intraocular pressure increases were required to
9 be reported as adverse events if they were significant by
10 the investigators, and there were four such cases reported
11 as adverse reactions. In three of these cases, intraocular
12 pressures were elevated to 26, 23, and 23. In all three of
13 these eyes, they resumed the baseline with simple cessation
14 of the topical steroid. There was, however, one eye that
15 had an intraocular pressure rise to a level of 45, and in
16 this eye it was treated with topical beta blockers and
17 returned to baseline within one month, and he's off all
18 medications and has not sustained a continued rise. The
19 visual field testing on this eye showed that there was no
20 visual field loss.

21 A haze formation reported as greater than Grade
22 2 was reported in this matter by our investigators, and
23 I'll talk a little bit about the grading system in a
24 second. At six months, two eyes were graded as Grade 2

1 haze, for an incidence of 1.9 percent, even though the best
2 spectacle corrected acuities in these eyes were 20/25. At
3 12 months there were a total of four eyes, for an incidence
4 of 4.3 percent, and in these four eyes only one was worse
5 than 20/40; one was 20/50, and three were 20/20. At the
6 final visit there was one eye, for an incidence of 1.2
7 percent, reported as having a Grade 2 haze.

8 Now, there are various methods of grading haze,
9 and one of the accepted methods that we actually used in
10 the PRK for moderate myopia study was that a Grade 2 haze
11 should interfere with refraction. So in my personal
12 grading system, several of these eyes could not have been
13 graded as a Grade 2 haze. We interpret that as the
14 investigator probably seeing a dense peripheral or arcuate
15 haze that he would have graded as Grade 2 in density, and
16 they were encouraged to, if anything, overreport. So even
17 though they didn't reduce best spectacle corrected
18 acuities, they were graded as a Grade 2 haze.

19 There was no significant change in endothelial
20 cell counts at any time point studied.

21 We did contrast sensitivity and glare testing
22 as a part of the study, and I would like to now call Dr.
23 Jerry Legerton, who is the Benedict Professor of Optometry
24 at the University of Houston and who has studied the

1 results of these two studies. I'd like to have him explain
2 these studies to us.

3 DR. LEGERTON: Thank you, Dr. Salz.

4 Good morning. I am as well a paid consultant
5 of VISX, Inc.

6 There were two non-routine clinical tests used
7 to assess the quality of vision as a measure of safety.
8 The first is that of contrast sensitivity that utilized the
9 vector vision CSV-1000. The investigators were asked to
10 grade the decrement in contrast sensitivity on four spatial
11 frequencies as a mild, moderate, or large loss. In the
12 submission report you received a frequency distribution, as
13 indicated on this table. Subsequently, to give greater
14 statistical understanding, the chi-square test was
15 administered to study the relationship between the
16 distribution of findings at follow-up visits relative to
17 the pretreatment distribution. As you will see by the chi-
18 square P values, there is no statistically significant
19 difference between the pretreatment and the postoperative
20 measurements at any follow-up visit.

21 It was also important to understand the
22 relationship between this test instrument and patient
23 responses to the subjective questionnaires that were
24 administered pretreatment and on follow up visit. As you

1 will see, there is no statistically significant
2 relationship between the findings of response to bright
3 light and to night vision at any point. There is a very
4 weak relationship as indicated by the R-squared values at
5 the 12-month and final visit for double vision and for
6 satisfaction at the 12-month and final visit.

7 It's important to note that these values are
8 very low, that the R-square would indicate that
9 approximately 12 percent and 11 percent of the change in
10 response to double vision could be explained by a change in
11 response on contrast sensitivity. On overall satisfaction
12 we in fact get even lower percentages. This would indicate
13 that contrast sensitivity is of little value in predicting
14 changes in patient response or in satisfaction, night
15 vision, double vision, et cetera.

16 We also studied glare using the brightness
17 acuity tester. The investigator was asked to report either
18 a normal or an abnormal response according to numerical
19 guidelines. Again, in the frequency distribution we gave
20 you in the study, we reported it as such and we followed
21 that up with the chi-square value, and there is no
22 statistically significant difference between the
23 pretreatment and post-treatment distributions.

24 ~~When the correlation was studied with the~~

1 linear regression analysis, at only the 6-month and 12-
2 month visit did we again get very low relationship of the
3 glare to a response of double vision, and only at the 6-
4 month visit approximately 14 percent of the overall
5 satisfaction could be explained by a change in glare
6 response. There was no statistically significant
7 relationship between the response to bright light on a
8 questionnaire and to night vision with the change in the
9 glare response.

10 Dr. Salz will continue to share with you on the
11 issue of patient questionnaires, because certainly
12 subjective responses are valuable.

13 In conclusion, we would say that as
14 administered in this study, the contrast sensitivity and
15 glare instruments are of little value in predicting patient
16 satisfaction and patient symptoms and outcome. Dr. Salz
17 will share with you again on the other patient
18 questionnaire issues.

19 DR. SALZ: We recognize the difficulty in
20 interpreting these glare and contrast sensitivity tests.
21 One other way to approach this was in the patient
22 questionnaire, where patients were asked specifically
23 whether they had difficulty with night vision

24 ~~preoperatively and then asked again at various time gates~~

1 after the procedure was performed. You can see that
2 preoperatively 31 percent of the patients said that they
3 did have difficulty with night vision. In the 6, 12, and
4 final visits, the percentage actually went down slightly.
5 So that certainly doesn't indicate that there was a higher
6 percentage that complained of increasing difficulty with
7 their night vision after this procedure was performed.

8 This is a summary of the adverse events that
9 are listed in Table 26 of the information that's been given
10 to you. These are adverse events as reported by our
11 investigators, and this was required at the time the study
12 was designed in 1992 and 1993. There were five cases of
13 lens opacities, which we've discussed previously. There
14 was the one case of a corneal infiltrate that we discussed
15 previously. There were the four intraocular pressure rises
16 that we've discussed, the three haze cases that we've
17 discussed, and in addition there were two complaints that
18 were subjective. One was a ghosting of the images, and I
19 believe one was of multiple images.

20 There were four cases of posterior pole
21 pathology noted that were not noted preoperatively. One
22 was a posterior vitreous detachment; one was peripheral
23 lattice noticed postoperatively without a hole; one was a
24 choroidal retinal scar; and there was one case where it was

1 noted that there was an increase in optic nerve cupping in
2 the treated eye. The same increase in optic nerve cupping
3 was described in the untreated eye, and there was no visual
4 field loss suggestive of glaucoma in that particular
5 patient.

6 There were also a number of miscellaneous
7 adverse reports reported by the investigators. We were
8 required to report anything that might have happened. For
9 example, if a patient even developed a haze during the
10 post-op period, you were supposed to put that down as an
11 adverse event. My one comment about these is living in Los
12 Angeles, the lids burning and stinging, there was only one
13 case, and I can't quite see how Peter McDonald only had one
14 patient complaining about that. In my practice it's 100
15 percent of them. So we don't feel that any of these
16 miscellaneous adverse events that were reported really had
17 much significance in either outcome or were even
18 necessarily procedure related.

19 Retreatments are another important aspect of a
20 safety analysis, and as in the PRK for low to moderate
21 myopia where it was established that it is not necessarily
22 undesirable to have a small undercorrection because we
23 showed that retreatments were quite effective and also
24 quite safe, in this study we had nine eyes that underwent a

1 retreatment. Five of those eyes underwent the retreatment
2 primarily for undercorrection, and in all five of those
3 eyes the original investigator had targeted the eye for a
4 small undercorrection and the patient was not satisfied
5 with the uncorrected postoperative acuity, and so those
6 five eyes were retreated.

7 In the other four eyes, the retreatment was
8 done for undercorrection plus a combination of either an
9 irregular videokeratography, a slight decentration, and in
10 one case abnormalities in videokeratography plus some
11 residual haze.

12 Let's look at the nine eyes that were retreated
13 and see how they did. If you look at the middle column, it
14 gives the uncorrected visual acuities after the primary
15 treatment but before the retreatment, and only one of those
16 eyes had an uncorrected acuity that was worse than 20/50,
17 and that eye was at 20/80. If you then look at the second
18 to the last column, the post-retreatment visual acuities,
19 you can see that all of the eyes were improved to an
20 uncorrected visual acuity of 20/30 or better, except the
21 eye that started at 20/80, and that eye improved to 20/50.

22 I think an even more important aspect of this
23 slide is the post-retreatment best spectacle corrected
24 visual acuities, which show that there was really no

1 significant reduction and all of these eyes ended up with
2 post-retreatment visual acuities, best corrected, between
3 20/15 and 20/25. So just as in the low to moderate myopia
4 study, I think we've demonstrated that retreatments are not
5 only quite successful but they also appear to be quite
6 safe.

7 One of the reviewers asked the sponsor to
8 address the issue of eyes that had losses of best spectacle
9 corrected visual acuity of equal to or greater than two
10 lines at any time point during the study, and these are
11 summarized in Tables 29 and 29X, which was a supplemental
12 table that was provided to you. There are 12 such eyes
13 that meet this criteria.

14 In the first category there were the lens
15 opacity cases, and the ones that led to losses of greater
16 than two lines, these patients had a progression of what
17 was initially described as an opacity becoming a cataract.
18 Both of those patients have subsequently had cataract
19 surgery and have returned to best spectacle corrected
20 visual acuities of 20/20 and 20/25.

21 There was another patient that developed a
22 cataract during the study, leading to a two line loss, but
23 he still has 20/30 vision and that patient has not had
24 cataract surgery.

1 We talked earlier about the patient with the
2 corneal infiltrate. At his worst he had a two line loss to
3 20/30 and has since recovered to 20/20.

4 There were four cases that had irregular
5 videokeratography, and one or two combined with haze that
6 led to at some time point two line losses of best spectacle
7 corrected visual acuity. It was requested that we get
8 these patients back for a subsequent exam, and that was
9 performed, and in these four eyes, two of them have best
10 spectacle corrected acuities of 20/25 and two of 20/20.

11 There were two cases where there was a
12 reduction of two lines and it was not explained either by
13 the slit lamp examination, the fundus examination, or by
14 videokeratography why this two line loss occurred. Those
15 eyes have ended up with best spectacle corrected acuities
16 of 20/30 in both cases.

17 Finally in the last column, there were two
18 patients who started with preoperative best spectacle
19 corrected acuities, one of 20/10 and one of 20/12.5, that
20 had temporary reductions to 20/20, representing a greater
21 than two line loss in those cases, and those eyes have
22 recovered to 20/20 and 20/15. So I think in summary even
23 though there were some two line losses during the study,
24 you can see by the updated and the last visit best

1 spectacle corrected acuities that certainly the majority of
2 these eyes have made a very nice recovery and have
3 satisfactory postoperative best spectacle corrected
4 acuities.

5 This summarizes the incidence of two line or
6 greater losses at the final visit and then the updated
7 visit that was requested of the sponsor to get some of
8 these patients back. So at the final visit the total
9 incidence would be 4.8 percent, and the updated visit
10 reduced to two eyes or 2.4 percent. This excludes the eyes
11 that had cataract surgery during the development of the
12 study.

13 It was also asked by a reviewer for us to
14 summarize the incidence of best spectacle corrected visual
15 acuity losses of equal to or greater than 20/40 at any time
16 point during the study. Again, there were five such eyes,
17 and these are summarized in the middle column as to what
18 their best spectacle corrected acuity loss was and when it
19 occurred. You can see they were all between 12 and 24
20 months, and they were all between 20/40 and 20/50 at their
21 worst. The column on the right then summarizes what their
22 final acuities were, and you can see that all of them
23 recovered to 20/25, or at worst to 20/40. We had one eye
24 in the entire study that ended up with the best spectacle

1 corrected acuity of 20/40, and the others recovered to
2 20/25 or 20/30.

3 Patient satisfaction is another way to analyze
4 this data. In other words, after we've done the procedure,
5 we asked the patients how satisfied were they with the
6 results of this procedure. They were asked to grade their
7 satisfaction response on a scale of 1 to 10, with 1 being
8 the least satisfied and 10 being highly satisfied. They
9 were given this questionnaire at 6 months, 12 months, and
10 the final visit. You can see from the column on the very
11 right that the mean scores for these three time gates were
12 8.3, 8.5, and 8.4, indicating certainly that the vast
13 majority of patients were quite satisfied with the results
14 of this procedure.

15 This satisfaction index was, in effect, quite
16 close to the report for the low to moderate myopia study
17 that was presented previously.

18 I think probably the most important summary
19 slide -- and this is my last slide in this part of the
20 presentation -- is this one, where we tried to compare the
21 panel safety guidelines supplied by the agency on October
22 10th of 1996 to this study that we're discussing.

23 The panel recommended guidelines for losses of
24 best spectacle corrected acuity of greater than two lines.

1 They recommended that the incidence be not higher than 5
2 percent. Our incidence was 4 percent.

3 They recommended that losses of best spectacle
4 corrected acuity of greater than 20/40 be 1 percent or
5 less. Ours was 1 percent.

6 They recommended that haze leading to loss of
7 best spectacle corrected acuity of greater than two lines
8 and persisting beyond six months be less than 1 percent.
9 Ours was 1 percent.

10 They recommended that we not induce refractive
11 astigmatism of greater than 2 diopters and that the
12 incidence be less than 5 percent. We actually had no cases
13 like that.

14 They recommended that sight-threatening adverse
15 events be limited to less than 1 percent. Our only sight-
16 threatening adverse event was the case of the corneal
17 infiltrate, which was peripheral and which recovered to a
18 best spectacle corrected acuity of 20/20.

19 So that's the formal part. As a refractive
20 surgeon I would just say that I think compared to the tools
21 that we now have available to us for correcting astigmatism
22 in the United States, which is incisional keratotomy, which
23 I have personally performed since 1980, and I've seen many
24 patients in consultation having incisional keratotomy, and

1 there are a variety of problems with that technique, as we
2 all know -- there are overcorrections, undercorrections,
3 misalignments of the axis, perforations and so forth -- I
4 truly believe after analyzing this data and having looked
5 at some of the foreign data that correcting these eyes with
6 the VISX excimer laser system offers us a chance at
7 definitely improving our outcomes in the correction of
8 astigmatism.

9 I thank you very much.

10 DR. ODRICH: Thank you, Dr. Salz.

11 VISX is fortunate in having Dr. Bruce Jackson
12 from the University of Ottawa Eye Institute here today to
13 talk about the correction of myopic astigmatism with the
14 VISX excimer laser system at the University of Ottawa.

15 Dr. Jackson?

16 DR. JACKSON: Thank you, Dr. Odrich.

17 Good morning. My expenses have been paid by
18 VISX for this panel meeting.

19 I am Professor and Chairman of the Department
20 of Ophthalmology at the University of Ottawa, and Director
21 General of the University of Ottawa Eye Institute at the
22 Ottawa General Hospital, and director of our excimer laser
23 research program. I'd like to acknowledge my coworkers,
24 Dr. Agapitos and Dr. Mintsicoulis. All three of us are

1 corneal specialists, and we have performed all of the
2 surgery at the University of Ottawa Eye Institute. I also
3 acknowledge our researchers.

4 Although we have been doing excimer laser
5 surgery and correction of astigmatism since 1993 and have
6 treated over 1,000 patients, all the results presented in
7 this analysis have been derived from data submitted in
8 November to the FDA.

9 I'd like to point out that our protocols have
10 been approved by the research ethics board of the Ottawa
11 General Hospital. We are the only university center in
12 Canada that has made refractive surgery a central theme and
13 has undertaken such studies. Every treated patient was
14 entered sequentially into a study protocol. All patients
15 signed and received a copy of our approved consent form,
16 and all patients are followed by corneal specialists. Our
17 protocols are monitored by our ethics review committee.

18 I am reporting on 95 eyes with 100 percent
19 follow-up at 12 months. All of these 95 eyes meet the U.S.
20 entry indications. Our mean preoperative sphere in this
21 group was -3.75 diopters, our mean preoperative astigmatism
22 was -1.33, and our mean preoperative spherical equivalent
23 was -4.41. Postoperatively at 12 months, our mean

24 ~~postoperative sphere was -0.16, our mean postoperative~~

1 astigmatism was -0.26 diopters, and our mean postoperative
2 spherical equivalent was -0.29 diopters. This means that
3 we achieved a reduction in the mean sphere of 95.7 percent,
4 in the astigmatism of 80.5 percent, and mean spherical
5 equivalent of 93.4 percent.

6 We had one eye, for 1 percent, which lost two
7 lines of best spectacle corrected visual acuity and
8 subsequently improved. No eye lost more than two lines of
9 best spectacle corrected visual acuity.

10 We achieved 20/20 or better in 67 percent of
11 our eyes, and 20/40 or better in 96 percent.

12 When we compare our data from the University of
13 Ottawa to that of the U.S. data, we achieved 20/40 or
14 better in 96 percent, compared to 88.1 percent, and two
15 lines or more best spectacle corrected visual acuity loss
16 of 1 percent, compared to 2.4 percent.

17 I and my colleagues have been treating
18 astigmatism now for three to four years at least, and have
19 been extremely satisfied with the results achieved with the
20 VISX excimer laser system. In fact, across Canada it's
21 routine, and down to -0.25 diopters a cylinder is routinely
22 treated. I was very surprised that the PRK approval
23 allowed the astigmatism of up to 1 diopter to be left
24 untreated. In my experience, and when we analyzed our

1 data, this group of patients between -0.25 and -0.75
2 diopters had a poorer uncorrected visual acuity, and also
3 had a slower recovery of uncorrected visual acuity compared
4 to when we treated even the lower levels of astigmatism.
5 We always treated 1 diopter or more.

6 I was also very surprised at a refractive
7 meeting that occurred just in December, sponsored by the
8 University of California at San Francisco, that so much
9 discussion was being made about how PRK can be combined
10 with astigmatic keratotomy. Here you're introducing a
11 whole new element of incisional surgery with its inherent
12 risks. It's unnecessary when one can really dial in the
13 parameters to treat astigmatism and do it at the same time.

14 Thank you very much.

15 DR. ODRICH: Thank you, Dr. Jackson.

16 We're also fortunate to have Dr. Julian
17 Stevens, who presented the efficacy data for the U.S.
18 study, and he will speak on the correction of myopic
19 astigmatism with the VISX excimer laser system and his
20 experience at Moorfields Eye Hospital. I'd like to
21 reiterate that this data has been given to the FDA in Excel
22 format in November and I believe was included in the
23 handouts.

24 Dr. Stevens?

1 DR. STEVENS: Thank you.

2 To analyze the data of the U.S. studies, and
3 also that from Moorfields Eye Hospital, we used a software
4 program called Vector Inspector, and I am the author of
5 that.

6 I am today the mouthpiece of a large team at
7 Moorfields of ophthalmologists who have been looking at
8 laser refractive surgery since 1990. We've had the
9 opportunity -- Moorfields has never owned a laser system.
10 We've actually had five lasers at Moorfields since 1990,
11 and the data I'm going to present today pertains to a
12 prospective study recruiting from 1993 to 1995.

13 This study was to a strict protocol. This
14 protocol was approved by the Moorfields research committee
15 and ethics committee. Every treated patient was entered
16 into the study protocol. It was a very strict protocol.
17 These were sequential treatments. All patients signed and
18 received a copy of the approved consent form, and all
19 patients were followed up after treatment at one week, one
20 month, three months, six months, 12 months, and then
21 annually for a five-year follow-up. This study is due for
22 completion in the year 2000.

23 Five hundred and thirty eyes exactly matched
24 the criteria for the U.S. multicenter study. This subset

1 data set is included today. 85.7 percent of these eyes
2 attended at 12 months, 454 of 530. The mean pretreatment
3 sphere was -3.74 diopters, and the mean pretreatment
4 astigmatism was -1.49 diopters. The spherical equivalent
5 then is -4.48.

6 At 12 months, the mean post-treatment sphere
7 was -0.14, and the mean post-treatment astigmatism was
8 reduced from -1.49 to -0.75. The mean spherical equivalent
9 was then -0.51.

10 What did we actually achieve in terms of our
11 intended correction? Our mean sphere, we achieved 96
12 percent of our intended, and the mean astigmatism was 50
13 percent of intended. The mean spherical equivalent was
14 then 89 percent of intended.

15 Three eyes, or 1 percent, lost two or more
16 lines of best spectacle corrected visual acuity, and two of
17 these three eyes lost more than two lines. Both of those
18 patients were graded as having severe haze.

19 For the uncorrected acuity targets, 20/20 or
20 better, 59 percent or 267 of 454 eyes achieved this visual
21 target. For an uncorrected acuity of 20/40 or better, 86
22 percent or 392 of 454 eyes.

23 Looking at 20/40 or better, the Moorfields data
24 shows that 86 percent achieved this, and for the U.S. data,

1 88.1 percent, which is remarkably similar. The two lines
2 or more loss of best spectacle corrected acuity, 1 percent
3 at Moorfields and 2.4 percent in the U.S. data. I think
4 the take-home message there is that it's very interesting
5 that this large international study, both from the
6 University of Oxford and Moorfields together with the U.S.
7 study, show remarkably concordant independent data.

8 So in summary, we have an application for up to
9 -6 diopters of myopia on the spectacle plane with -0.75
10 diopters to 4 diopters of astigmatism on the spectacle
11 plane.

12 This is the end of my presentation. Thank you.

13 DR. ODRICH: Thank you, Julian.

14 Both presentations of Dr. Jackson and Dr.
15 Stevens, their patients, those 530 that Dr. Stevens
16 presented and the Jackson patients of 95, are identical
17 patients to the indication here. Those were taken from the
18 large handouts that were given to the panel and were
19 analyzed, and the data you have in those four or five
20 slides that each of the doctors presented match identically
21 the indication of zero to -6 diopters of spherical myopia
22 at the spectacle plane with concomitant astigmatism of
23 -0.75 to -4 diopters.

24 ~~The breakdown, as I showed before, is this.~~

1 These were treated on identical lasers. The system as
2 approved in the United States requires only a radial
3 asymmetric beam with no increase in the central ablation
4 depth as compared to the approved indication in the United
5 States.

6 This summary slide which shows the last visit
7 in the United States, which is at 20 months or longer, the
8 last visit of the Canadian group of 95, which is 12 months,
9 and the U.K. data of visits at 12 months, shows the
10 following comparison: 88 percent of the U.S. patients
11 achieved the uncorrected acuity of 20/40, 96 percent of the
12 Canadian patients, and 86 percent of the U.K. patients.
13 BSCVA losses, when rounded to single integers, are 2
14 percent, 1 percent, and 1 percent. Finally, the reduction
15 of astigmatism as a scalar quantity -- this is not taken as
16 a vector quantity but as a scalar quantity -- are reduced
17 at final visit -- and again, that's at 20 months or better
18 for the U.S. -- to 64 percent, 81 percent for the Canadian
19 University of Ottawa study, and for the Moorfields data a
20 50 percent reduction.

21 We'd like to remind the panel that we are
22 asking for approval for the treatment of spherical myopia
23 of plano to -6, and from 0.75 to 4 diopters of cylinder.

24 Thank you.

1 DR. WILKINSON: That ends the discussion?

2 MR. PATINO: Yes, that ends our presentation.

3 DR. WILKINSON: Thank you for a very clear and
4 concise tag team presentation. It was very clear.

5 Right now we're going to take a brief break
6 before the agency presentation. Please be in your seats
7 promptly at 10:30. I have 10:16 or 10:17 right now. We'll
8 begin promptly at 10:30.

9 (Recess.)

10 DR. WILKINSON: We'll resume the discussion on
11 P930016/S3, and we'll begin with the clinical review by our
12 in-house reviewer, Dr. Malvina Eydelman.

13 DR. EYDELMAN: Good morning, ladies and
14 gentlemen. In my presentation today I would like to
15 summarize some of the points from my written review which
16 you have previously received, as well as some additional
17 analysis from the information that the sponsor has
18 submitted since the primary mailout and which you have
19 received in the second and third mailouts. The information
20 was updated with the latest numbers that were officially
21 submitted to FDA.

22 The refractive keratectomy for astigmatism
23 using the VISX excimer laser system is intended for use in
24 patients seeking elimination or reduction of mild to

1 moderate myopia of between zero and 6 diopters spherical
2 myopia at the spectacle plane, and concomitant elimination
3 or reduction of astigmatism of not less than 0.75 and not
4 more than 4 diopters at the spectacle plane as determined
5 by minus cylinder refraction.

6 It is indicated in patients with a change in
7 manifest refraction of less than or equal to half a diopter
8 per year, and in patients who are 18 years of age or older.

9 The specifications of the VISX excimer laser
10 system used for correction of astigmatic refractive errors
11 are identical to the currently approved VISX excimer laser
12 system PRK for mild to moderate myopia and PTK. The
13 laser's wavelength is 193 nanometers. The repetition rate
14 is 5 hertz. Fluence at the corneal plane is 160, and the
15 beam is spatially and temporally integrated. Except for
16 the modified key cards, there is no software required to
17 treat astigmatism. There is no new software required to
18 treat astigmatism with this system. The system requires no
19 additional hardware pieces. The calibration procedure is
20 identical to PTK and PRK low to moderate myopia.

21 An ablation of 6 diopters of sphere, with 4
22 diopters of cylinder, would result in an ablation depth
23 that is not greater than 6 diopters of sphere treated
24 alone, which is the upper limit of the approved VISX PRK

1 system for mild to moderate myopia.

2 It is important to note that even though the
3 ablation depth and beam characteristics are identical to
4 the approved system for low to moderate myopia, there is
5 one major point of difference. The minimum diopter of
6 optical zone for the low to moderate myopia indication is 6
7 millimeters, while the optical zone of astigmatic ablation
8 may have a minor axis as small as 4.24 millimeters. Thus,
9 one would anticipate glare, contrast sensitivity, and
10 problems with night vision to be additional safety concerns
11 associated with this ablation profile, especially in
12 subjects with larger pupils.

13 The sponsor is seeking approval of the VISX
14 excimer laser system for the correction of astigmatic
15 refractive errors based on the clinical results of the U.S.
16 clinical study performed under the IDE and further
17 substantiated with international data from Canada and the
18 U.K.

19 One hundred thirty-three eyes were treated in
20 the U.S. clinical trial. Enrollment and treatment was
21 limited to five institutions and 75 subjects. The
22 refractive inclusion criteria specified that the primary
23 eye have 1 to 6 diopters of spherical equivalence, with
24 0.75 to 4.5 diopters of cylinder. Twelve primary eyes

1 exceeded the preoperative limit on spherical equivalence.

2 The protocol as written under the IDE did not
3 require fellow eyes to meet refractive eligibility. Thus,
4 even though there were 12 fellow eyes that did not meet
5 refractive eligibility imposed by the protocol on primary
6 eyes, they are not considered protocol violations.

7 The original PMA submitted in August of 1996
8 had data analysis of 133 eyes, and all of them had the
9 proposed refractive indications that were identical to the
10 refractive indications of the protocol. We have reviewed
11 the original submission and pointed out to VISX that 18
12 percent of the eyes that were being analyzed were outside
13 the refractive indications that were being pursued. It was
14 also pointed out that there was only one subject treated
15 with astigmatism above 4 diopters, which made it difficult
16 to substantiate approval of an indication of astigmatic
17 ablation as high as 4.5.

18 Having considered FDA's concerns, VISX has
19 resubmitted the data, analyzed only to include patients
20 with up to 6 diopters of spherical myopia and between 0.75
21 and 4 diopters of refractive cylinder at the spectacle
22 plane. These refined indications resulted in a cohort of
23 116 eyes.

24 ~~It is of interest to note that even though~~

1 proposed indications specify subjects 18 years or older,
2 the youngest subject treated in the U.S. was 24 years old,
3 and the mean was 39.5. Both the Canadian and U.K. studies
4 indicate starting ages of 21. Since age is known to be
5 related to the maximum pupillary size, one can postulate
6 that the decreased optical zone of treatment would be more
7 problematic in younger subjects. This should be kept in
8 mind when appropriate age for indications is considered.

9 This table reveals that the majority of
10 subjects treated, 62 out of 116, had 1.1 to 2 diopters of
11 preoperative cylinder, and only six subjects had 3.1 to 4
12 diopters of preoperative cylinder.

13 The results of 108 eyes out of 116 treated were
14 included in the analysis at six months, thus giving us 93
15 percent accountability. Ninety-two eyes were available for
16 analysis at one year, and 84 of the cohort was examined at
17 two years.

18 If we look at the results of uncorrected visual
19 acuity for 20/20 or better, it was achieved in 36 percent
20 of eyes at 6 months, 46 percent at 12 months, and 40
21 percent at the final visit. The percentage of eyes
22 achieving 20/40 or better remains stable at around 87
23 percent throughout the duration of the study.

24 ~~If one looks at the uncorrected visual acuity~~

1 results stratified by preoperative cylinder, it is
2 interesting to note that no subjects in the 3.1 to 4
3 diopter group achieved 20/20 uncorrected visual acuity.
4 One must keep in mind, however, that there were only six
5 eyes available in that range for analysis at six months,
6 and thus the validity of any conclusions would have to be
7 questioned.

8 Best spectacle corrected visual acuity is
9 compared in this graph to preoperative, 6 months, 12
10 months, and final visit. No eye was worse than 20/30
11 pretreatment, but some losses did occur and can be better
12 appreciated by the next graph. Here the numbers of lines
13 lost are plotted for 6 months, 12 months, and the final
14 visit. It is interesting to note that the percentage of
15 eyes with a loss of greater than one and less than or equal
16 to two lines of loss has remained relatively stable over
17 time, while the number of subjects with a greater than two
18 line loss increased with time.

19 Efficacy of the spherical equivalent correction
20 was 93.5 percent at six months, 95.6 percent at 12 months,
21 and 92.9 percent at the final visit. The mean reduction in
22 absolute cylinder was 67 percent at six months, 64 percent
23 at 12 months, and 62 percent at the final visit.

24 ~~Eleven percent of eyes at 6 and 12 months, and~~

1 8 percent of eyes at the last visit had an axis shift of
2 greater than 30 degrees. Analysis of patient I.D.'s
3 reveals that subjects with axis errors greater than 30 at
4 six months are often not the same subjects as the ones
5 whose axis error was greater than 30 at later visits due to
6 the axis shift continuing over time. Thus, a total of 22
7 eyes out of 116 treated had an axis shift of greater than
8 30 at 6, 12, or 24 months.

9 Looking at some of the efficacy parameters
10 stratified by preoperative cylinder, we can see that while
11 spherical equivalent reduction was very similar for the
12 four subgroups, reduction of the absolute value of the
13 cylinder was 56 percent for the 0.75 to 1 diopter group, as
14 compared to 69, 76, and 71 for the others. Axis shift of
15 greater than 30 degrees was seen more frequently in the
16 0.75 to 1 diopter group, at 15 percent, as compared to 12
17 and 7 for the other groups.

18 Vector analysis has been described, and I'll
19 just add that they did reveal good overall stability over
20 time for all the endpoints. Vector analysis results for
21 efficacy of correction of cylinder were 94 percent for the
22 0.75 to 1 diopter group, as compared to 86, 80, and 79 for
23 the others.

24 ~~Now I'll talk a little bit about some of the~~

1 other safety parameters. Endothelial cell study was
2 performed, and no statistically significant changes were
3 observed.

4 I have already mentioned changes in best
5 spectacle corrected visual acuity. This slide concentrates
6 on it again from the accepted safety endpoint of loss of
7 two or greater lines. As you can see, at six months this
8 occurred in 4.8 percent, increasing to 6.7 percent and 8.5
9 percent later. If we take into account three non-corneal
10 losses and one report error, we're still left with 4.8
11 percent.

12 Corneal haze reached its maximum of 4.3 percent
13 at 12 months. Breaking up the corneal haze rate occurrence
14 by preoperative cylinder reveals that all the cases
15 occurred only in the 0.75 to 1 diopter group, reaching 15
16 percent for these subjects at 12 months.

17 The contrast sensitivity measurements in this
18 protocol were carried out only under photopic conditions.
19 Compared to pre-op, which is graphed here in pink, we can
20 see an increase in mild loss from 6 to 9 percent at six
21 months, 13 percent at 12 months, and decreasing by final
22 visit. Moderate loss continued to increase throughout the
23 post-op period.

24 ~~Loss of two or more lines of acuity was~~

1 considered to be an abnormal glare response. If we
2 adjusted percentages for the subjects for whom this
3 information was not available, at six months and 12 months
4 we see an increase from 2 percent to 6 and 7 percents.
5 However, at the time of the last visit, no subject had an
6 abnormal glare response.

7 Looking at the glare response by pre-op
8 cylinder, we see that the 0.75 to 1 diopter group had the
9 largest losses.

10 Double vision occurred in 5.6, 5.4, and 5.9
11 percent of subjects over time. Sensitivity to bright light
12 was reported by 16.7 percent of subjects at six months, 13
13 percent at 12 months, and 15.5 percent at the final visit.
14 Difficulty with night vision was reported by 26 percent at
15 six months, and at the last visit 23 percent were still
16 symptomatic.

17 Now just a few words about the Canadian study.
18 Data from 95 eyes followed for 12 months under the same
19 protocol as U.S. was submitted to the agency. In this
20 study most subjects were in the higher preoperative
21 cylinder group.

22 The U.K. study analysis was submitted as well.
23 Refractive characteristics of these eyes were different
24 than in the U.S. cohort, with myopic sphere limit not

1 reaching 6 diopters, and with cylinders starting at less
2 than 0.5 diopters instead of 0.75.

3 Most U.K. subjects had less than 0.5 diopters
4 of pre-op cylinder. 0.5 to 0.9 diopters was the next
5 largest group of subjects. Unfortunately, the subject
6 analysis was not broken up into comparable groups to U.S.,
7 and we do not know how many of these 179 eyes had less than
8 0.75 diopters of cylinder.

9 Comparing results of these three studies, we
10 can see that even though the percentage of eyes with 20/40
11 or better uncorrected visual acuity at six months was
12 comparable, a much lower percentage of U.S.-treated eyes
13 were able to achieve 20/20 or better.

14 When we analyze uncorrected visual acuity
15 results by pre-op cylinder, we see the greatest
16 discrepancies for subjects with 3.1 to 4 diopters of
17 preoperative cylinder. The U.S. study consistently
18 resulted in lower uncorrected visual acuity across all
19 these sub-groups.

20 The U.S. study also demonstrated a larger loss
21 of best spectacle corrected visual acuity than its
22 international counterparts. If we look only at loss of
23 greater or equal to two lines of best spectacle corrected
24 visual acuity, it's interesting to see that in the

1 information presented to the agency, no cases for the U.K.,
2 and higher rates for U.S. than Canada.

3 Since this is a first astigmatic PRK brought
4 for panel consideration, we wanted to summarize some of the
5 major differences between this system and its myopic
6 counterpart so as to get your guidance on the rates of
7 efficacy and safety outcomes for astigmatic PRK which you
8 feel are acceptable for the patients undergoing this
9 procedure.

10 Here you can see that for astigmatism at six
11 months, 35.8 percent of eyes achieved 20/20 or better
12 uncorrected, while for low to moderate myopia the number
13 was 55.8. At 12 months it's 45.6 versus 63.7, and at 24
14 months it's 40.2 versus 58.3. When we look at uncorrected
15 visual acuity of greater or equal to 20/40, the numbers are
16 a little closer. At six months it's 86.8 versus 94.5, at
17 12 months 86.7 versus 95.1, and at 24 months 86.6 versus
18 93.7.

19 Now here I have best spectacle corrected visual
20 acuity loss of greater or equal to two lines from the U.S.
21 study only. At six months for astigmatism it was 4.8
22 percent as compared to 2.3 percent for low to moderate
23 myopia, at twelve months it's 6.7 percent versus 2.1
24 percent, and at 24 months, regardless whether you take into

1 consideration the three eyes that were due to non-corneal
2 errors -- so if you look at 8.5 or 4.8, either one of those
3 numbers is significantly larger than 0.2.

4 Abnormal glare. In astigmatism at six months,
5 5.5 percent. Low to moderate myopia, 1 percent. Twelve
6 months, astigmatism, 6.5. Low to moderate myopia, 1.6. By
7 24 months, neither one has reported abnormal glare.

8 Difficulty with night vision. Again, there's
9 quite a big difference between the numbers that we see.
10 Six months, 25.9 versus 4.8; 17.4 versus 5.2 at 12 months;
11 and 21.4 versus 3.9 at 24 months.

12 Sensitivity to bright light. Astigmatism,
13 16.7. Low to moderate myopia, 4.1. Twelve months, 12
14 percent versus 4.8, and at the final visit, 15.5 versus 3.

15 Double vision. Six months, astigmatism, 4.6.
16 Low to moderate myopia, 2.7. Twelve months, 5.4 versus
17 1.5, and at the final visit, 5.9 versus 1.3.

18 Keeping in mind all that information, I would
19 now like to draw your attention to the questions in your
20 packets.

21 Question number 1: Based upon the 116 cohort
22 eyes treated in the U.S. clinical investigation, together
23 with the international data used as supporting evidence,
24 has VISX provided reasonable assurance of safety and

1 effectiveness of this device for the correction of
2 astigmatism?

3 Question number 2: Do the percent losses of
4 more than two lines of best spectacle corrected visual
5 acuity at 6 months, 12 months, and at the final visit in
6 this data provide reasonable assurance of the safety of
7 this device?

8 Question number 3: Do the safety and
9 effectiveness outcomes stratified by diopter of
10 preoperative cylinder of 0.75 to 1, 1.1 to 2, 2.1 to 3, and
11 3.1 to 4 support approval for the full range of astigmatism
12 of 0.75 to 4 diopters?

13 Question number 4: Do the reports and testing
14 results on contrast sensitivity, glare, double vision,
15 night vision difficulties, and sensitivity to bright lights
16 provide reasonable assurance of safety and effectiveness of
17 this device?

18 Question number 5: Is 18 years of age an
19 acceptable lower limit for this indication?

20 Thank you very much for your attention.

21 DR. WILKINSON: Thank you, Dr. Eydelman.

22 DR. WAXLER: This completes FDA's presentation.

23 DR. WILKINSON: Thank you, Dr. Waxler.

24 We'll move now to the two primary reviewers on

1 the panel for this PMA. I'd like to ask the primary
2 reviewers to not only give us the essence of their written
3 reports, but to be sure and comment on the questions raised
4 by Dr. Eydelman. I'd like to get a good feeling about how
5 you feel about the PMA in general and then some specific
6 answers to these questions.

7 We'll begin with Dr. Van Meter.

8 DR. VAN METER: Thank you, Pat.

9 My commendations go to VISX for trying to get
10 all the data in that was requested on time. There was a
11 lot of data that came in at the last few weeks. This was a
12 burden for the FDA, and likewise my compliments to the FDA
13 in general and to Dr. Eydelman in particular for an
14 excellent review.

15 I will not repeat the data but summarize my
16 comments. The VISX 20/20 laser system effectively reduces
17 myopic astigmatism. The main reduction of absolute
18 cylinder was 67 percent at six months, 64 percent at 12
19 months, and 62 percent at final visit. Subsequently, the
20 data on absolute cylinder has been stratified by
21 preoperative diopters of astigmatism, and some of my
22 comments will address the problems that I see with the
23 lower levels of astigmatism and the higher levels of
24 astigmatism.

1 The optical zone across the minor axis of
2 astigmatic ablation can be as small as 4.24 millimeters,
3 and this seems to correlate with the increased subjective
4 complaints in patients at night and patients who may have
5 larger pupils. There is some correlation of larger pupil
6 size in young patients, and the 18-year-old cutoff at the
7 lower end of the age range is probably too low. In the
8 U.S. study the youngest patient was 24 years old. The
9 youngest foreign patient was 21 years old, I believe.

10 The loss of two or more lines of best corrected
11 visual acuity was adjusted to 4.8 percent at 24 months.
12 This is within the FDA guidance document of 5.0 percent.
13 However, there is still some loss of best corrected
14 spectacle acuity that is of concern.

15 The loss of best spectacle corrected acuity in
16 patients with minimal myopia raises some concern to me
17 about the ultimate benefit of this procedure in treating
18 myopia of 1.0 and 0.75 diopters. These patients with lower
19 cylinder are less likely to be debilitated by their
20 astigmatism, and I think because there is a lower benefit-
21 to-risk ratio with these patients, that some attention
22 should be made to getting these lower astigmatic patients
23 in line. I don't think treatment of 0.75 diopters of
24 correction is justified by the data that is submitted.

1 The lack of 24-month data on any patient with
2 greater than 3.0 diopters makes it very difficult to assume
3 the efficacy or safety in this range of correction. Six of
4 116 patients were treated in this range. We have 12-month
5 data on three patients, and my feeling is that additional
6 data should be corrected for greater than 3.0 diopters.

7 A number of patients subjectively complained of
8 scotopic symptoms, and contrast sensitivity apparently was
9 performed only in photopic conditions. This would make it
10 difficult to actually realize the problems that these
11 patients see driving at night or the patients with larger
12 pupils might have. I don't think that this necessarily
13 requires more data, but I think it should be an informed
14 consent issue and will be a very pertinent factor as we
15 decide the age limits suitable for approval.

16 It's hard to grandfather in the patients with
17 greater than 3 diopters of astigmatism based on foreign
18 data alone. I notice the data from Moorfields' two
19 patients greater than, I believe, 3.0 diopters, and it
20 didn't stratify them additionally. I believe that
21 conceivably these patients with higher diopters of
22 astigmatism will benefit more from laser therapy than
23 patients with lower diopters of astigmatism. We just don't
24 have the data to do it.

1 My recommendations, based on the data that we
2 have, are that I think it is reasonable to approve. This
3 is not a motion, but my recommendation is that we approve
4 treatment for patients greater than 1.0 diopters up to 3.0
5 diopters. We have additional data collection on patients
6 with greater than 3.1 diopters of astigmatism and greater,
7 and that a higher age limit than 18, somewhere between
8 perhaps 24 and 30 years old, be appropriate for the
9 youngest age.

10 In summary, I suppose we all know that if you
11 take the ideal procedure, use it in the ideal fashion on
12 the ideal patient, then we have no complications. But as
13 we approach the treatment of astigmatism with this fairly
14 effective technology, I think it's safe to assume that we
15 don't always do the ideal procedure, and sometimes we don't
16 always do it on the ideal patient. It would be prudent for
17 us to not move too fast but yet to move as we decide who
18 and why we wish to treat.

19 Thank you.

20 DR. WILKINSON: Thank you.

21 We'll move on now to Dr. McCulley.

22 DR. McCULLEY: My comments and opinions are
23 very close to those of Dr. Van Meter's, with a few

24 exceptions. I'll just read my review. I think Woody did a

1 very nice job of summarizing. I would like to read mine, I
2 guess.

3 This application was reviewed with the mindset
4 of analysis for preponderance of data. I guess I've been
5 watching too much TV and seeing the difference between
6 civil and criminal trials.

7 (Laughter.)

8 DR. McCULLEY: Seeking reasonable assurance --
9 reasonable assurance -- of safety and efficacy as opposed
10 to the standards that I would have applied if I'd been
11 reviewing a class one peer review journal. An attempt was
12 made to make realistic, pragmatic, scientific approaches,
13 as opposed to a pure ivory tower approach.

14 I also would like to compliment Dr. Malvina
15 Eydelman. She did just a super job in reviewing this and
16 presenting it to us in written form, and her presentation
17 was excellent today. That helps a lot, saves a lot of
18 time, makes it a lot easier.

19 The sponsor did a better job with this
20 submission compared to the previous PRK submission.
21 However, the application still was somewhat difficult to
22 assess with ease, comfort, and with a lack of frustration.

23 The sponsor submitted data on, as best I could
24 tell, 100 assessable eyes for the United States with six

1 month follow-up, 84 with two-year follow-up, along with
2 supplemental data from Canada and the U.K. Since the N's
3 at 6, 12, and 24 months were different -- in other words,
4 108, 92, and 84 respectively -- the percentages that were
5 presented both in writing and in verbal presentations today
6 are less than ideally meaningful, and it's difficult to
7 know exactly how to assess that and what conclusions to
8 draw. I think one can draw positive conclusions from it
9 and negative conclusions.

10 The company I think did provide us, then, with
11 an analysis, over time, of the 84 that went through. My
12 impression is that those percentages that looked like they
13 could be interpreted negatively as showing a progressive
14 negative or bad effect were not borne out.

15 Before proceeding with specific safety and
16 efficacy issues, I'd like to point out that there are
17 several issues that are arising correcting myopic
18 astigmatism that are different from those encountered for
19 spherical correction alone. It's more difficult to
20 determine accurately the magnitude and axis of lower
21 cylindrical correction. In other words, it's more
22 difficult to determine accurately a 0.75 to a 1 diopter
23 than it is a 4 diopter cylinder. Therefore, there is
24 greater inherent error preoperatively, which will be

1 translated to problems postoperatively.

2 It can also be assumed that there will be a
3 greater effect of surface remodeling after PRKa on the
4 lower attempted cylindrical corrections, which seems to be
5 borne out in the postoperative data. With a smaller
6 diameter of the minor axis of correction, the importance of
7 accurate centration increases. Similarly, with the axis of
8 astigmatic correction being introduced, centration is
9 further increased in importance.

10 There is also another variable of aligning the
11 cylindrical correction from the laser with the cornea,
12 which introduces yet another variable. In other words,
13 PRKa is inherently a more difficult procedure to perform
14 than PRK.

15 So I'm not surprised, given those two concerns,
16 that there are a few more problems and that if one compares
17 PRKa to PRK, that the percentages don't look quite as good.
18 That's, quite honestly, to be expected, given the nature of
19 the patient being treated and the nature of the procedure.
20 So I guess I would be bothered if it looked better. So I
21 would expect that it wouldn't look quite as good.

22 From a safety standpoint, the loss of two or
23 more lines of best corrected visual acuity, the percentages
24 of patients who lost two or more lines of best corrected

1 visual acuity was greater at each time point than for PRK.
2 It should be noted that the numbers are significantly
3 smaller in this study in both the numerator and
4 denominator. There are only four eyes with less than 20/40
5 visual acuity at 12 months, three in the 0.75 to 1, and one
6 in the 1.1 to 2 diopter group; one at six months in the
7 0.75 to 1 group; and one at 24 months in the 1.1 to 2
8 group, which was 20/40 minus one. There was only one other
9 eye that was less than 20/30 at the 24-month period, with
10 all others having better visual acuity.

11 It would be useful to look at the individuals
12 who had 20/30 or 20/40 at any one point, and the company
13 has done that and presented that data to us, both in
14 written form prior to this meeting and at this meeting.
15 That decreases, in effect, or gives us a percentage of
16 patients with two or more lines lost that is significantly
17 less than was presented in the original submission.

18 Considering the small numbers of patients who
19 experience difficulty and the apparent resolution over time
20 in the majority of patients, with the additional data from
21 the U.K. indicating no patients with more than one line of
22 best spectacle corrected loss, and the data from Canada
23 with patients with no greater than two lines of best
24 spectacle corrected visual acuity at two years, my

1 assessment is that the risk does appear to be minimally
2 increased for PRKa for reasons that were stated in the
3 introduction, but that the risk is acceptable and
4 appropriate with informed consent by patients prior to the
5 surgery.

6 So I guess I feel a little bit differently. I
7 think that the full range is acceptable when one takes all
8 things into consideration.

9 Contrast sensitivity, glare difficulty,
10 problems with night vision -- I think here I will summarize
11 rather than reading. It's not surprising that there are
12 increased problems in these areas because of the 4.24 to
13 4.5 millimeter minor axis. I think as well my assessment
14 here is that -- I would have one question. The percentages
15 are up to 20 percent in some of these in problems with
16 night vision, but from a functional standpoint, how many of
17 those patients had problems functioning? There is a
18 complaint, and then there is a problem with function.

19 I haven't seen any comment about problems with
20 function. Problems of complaints, okay -- 20 percent.
21 That is, quite honestly, not all that surprising with the
22 smaller axis. Unless you find some other way of dealing
23 with astigmatic correction than that, then this is
24 something that's going to be inherent in this procedure.

1 My assessment here is that it's acceptable as
2 well so long as patients are adequately informed prior to
3 having the procedure done, and we'll talk about age and
4 pupillary size again in a moment. But I would like to
5 hear, so that one can inform patients effectively, how many
6 of those 20 percent indeed had problems functioning.

7 Efficacy, the uncorrected visual acuity, the
8 percentage of patients in the 20/20 to 20/40 range in the
9 U.S. study was somewhat less for PRKa than the PRK trials.
10 The U.K. data on a larger number of patients was somewhat
11 better, but still less than PRK.

12 It should be noted that a number of patients in
13 this study were targeted for undercorrection, some of whom
14 monovision. It also appears that the 3.1 program
15 consistently undercorrects sphere and cylinder, with a
16 greater tendency for undercorrection for the cylinder than
17 for the sphere. This is borne out in the international
18 studies as well.

19 From a safety standpoint, this approach to me
20 seems perfectly defensible. It's not surprising that the
21 results are somewhat less good for PRKa versus PRK because
22 of the increase in the complexity of the procedure and the
23 necessity for accuracy of refraction and centration. The
24 ~~patients treated with PRKa certainly fared better than they~~

1 would have had they been treated with PRK alone, leaving
2 their astigmatism in place, or in combination with
3 supplemental incisional surgery. Their outcomes approach
4 those of patients who were good candidates for PRK and
5 received PRK. Therefore, I am again comfortable with the
6 degree of uncorrected visual acuity that was obtained in
7 this procedure.

8 Cylindrical reduction -- I can go into more
9 detail but I think I'll just summarize. Again,
10 undercorrection was targeted, a good reduction in cylinder
11 was obtained, and again I felt that the results that were
12 obtained were certainly within an acceptable range.

13 Axis shift post-PRKa, the axes do appear to
14 shift over time, especially with the lesser intended
15 corrections, with IRCs of -- I'm not sure I like that
16 acronym -- with intended refractive corrections of 0.75 to
17 1 and 1.1 to 2, and less so with higher intended
18 corrections.

19 However, the magnitude of the shifting cylinder
20 appears to be low. One must therefore assume that there is
21 remodeling over time after PRKa, which can be measured by
22 axis shift, a phenomenon which is probably not surprising.
23 This does not appear to translate into significant clinical
24 problems, but does require, I think, postmarket

1 surveillance.

2 So it appears that the axis shifts, but it's a
3 very small cylinder that's shifting. If one looks at the
4 individual patient over time, a number of these -- and the
5 company did this in looking at those patients that had the
6 shifts -- a number of those patients that had a 30-degree
7 shift, for instance at six months, ended up with their axis
8 shifting back very close to what it was prior to treatment,
9 and it's a quarter to a half diopter shift.

10 So again, we kind of fall into the trap of
11 we've got small numbers, and if one plays the percentages
12 with that, then that can be misleading. In these axis
13 shifts, yes, there are axis shifts, but they appear to be
14 very small cylinders that are shifting, and I could not
15 find any evidence that that seems to translate into real
16 problems. So it might bother us mathematically, but I'm
17 not sure it should bother us clinically.

18 The issues raised by the FDA, I think there was
19 a question about needing further analysis of the Canadian
20 and U.K. data. I was able to use the Canadian and U.K.
21 data in areas where I needed it. There wasn't a full
22 analysis of it. That would have been nice, but I think I
23 was able to review the application without it.

24 ~~In terms of the adequacy of the numbers in the~~

1 cohort, even though the numbers aren't great, with the
2 length of follow-up and the supplemental data from
3 international sources, I think the number of patients that
4 are available for consideration is sufficient for me to
5 form an opinion relative to safety and efficacy.

6 In terms of the range, the -0.75 to 1 diopter
7 cylinder, my view is if one looks at the absolute numbers
8 and not percentages, that safety and efficacy in this range
9 is acceptable. I would be comfortable recommending its
10 inclusion so long as surgeon training and certification are
11 required and that in the training there is stressed the
12 need for absolutely accurate preoperative refraction and
13 precision of operative centration and axis alignment.

14 The patients with 3.1 to 4 diopters of
15 cylinder, if one combines the U.S. and U.K. data, I think
16 there are sufficient numbers to assess safety and efficacy
17 at a reasonable level. Again, I would require training and
18 certification as a condition attached to this opinion.

19 The lower age limit with the U.S. study
20 entering no patients less than 24 and the limited Canada
21 and U.K. being 21, my recommendation is that the minimal
22 age limit be set at 21, with an added label warning for
23 patients 21 to 30 relative to the increased risk for glare
24 and associated problems.

1 I thank Dr. Eydelman for finding the reference
2 to the fact that people, on average, don't tend to reach a
3 stable pupillary diameter of 4 millimeters until 30 years
4 of age. I think I intuitively knew some of that, but I
5 didn't recognize or wasn't aware of that specific
6 reference. It's a very useful piece of information that I
7 can use in informing patients.

8 Some additional concerns that I have about the
9 protocol design that arose from my review. I question the
10 advisability of allowing subjects to enter into a study
11 when bilateral therapy is ultimately desirable, when the
12 second eye does not meet the inclusion criteria. The
13 second area of concern relates to the advisability of
14 allowing patients to be entered into a study such as those
15 when lens opacities are noticed preoperatively. That, I
16 guess, is for future reference. It doesn't have a lot to
17 do with our review of this today.

18 The conditions for my recommendation for
19 approval, which are basically for as-requested, with the
20 exception of the age limit being set at 21, carry three
21 things. One relates to the informed consent, and that is
22 there's an increased risk for loss of two or more lines of
23 best spectacle corrected visual acuity. The second is the
24 increased risk for glare, especially in patients less than

1 30 years of age.

2 The second is recommendations for postmarket
3 surveillance in the areas of loss of best spectacle
4 corrected visual acuity, increased glare, halo, starbursts,
5 and assessment of axis shift.

6 The third is that there be user certification
7 because of the new issues and demands relative to PRKa. I
8 think it is essential that certified PRK surgeons be
9 additionally trained and certified for PRKa, with specific
10 emphasis on the needs for determination of pupillary
11 diameter, accuracy of preoperative refraction, and the
12 necessity of and technique for centration and axis
13 alignment.

14 DR. WILKINSON: Jim, do you have a burning
15 question that you want answered now, or should we kick this
16 around the table before asking?

17 DR. McCULLEY: No. I raised the one issue
18 about the 20 percent glare, the light sensitivity issues,
19 the question about how that translates into patient
20 function. Then the only other one I had in looking at the
21 data that came more recently is that there appeared to be,
22 from the topographic analysis, 32 percent decentration. I
23 found that to be remarkable.

24 DR. WILKINSON: Thank you.

1 Dr. Rosenthal?

2 DR. ROSENTHAL: Mr. Chairman, may I just make
3 one comment before the remainder of the discussion?

4 Members of my division have noted that there
5 are discrepancies between some of the data, and I think
6 they are minor discrepancies, between some of the data that
7 was presented by VISX and some of the data which was
8 presented to the agency for this panel meeting. I
9 therefore want to make sure that everyone realizes that the
10 resolution of these discrepancies must take place before a
11 final action will be taken by the agency.

12 DR. WILKINSON: Thank you.

13 DR. BULLIMORE: Can we ask what the nature of
14 the discrepancies are?

15 DR. ROSENTHAL: I think it's unfair to ask our
16 reviewers to be able to analyze the presentation online, so
17 to speak, but I think they are in the area of the glare and
18 contrast sensitivity.

19 DR. BULLIMORE: Okay. Thank you for that
20 clarification.

21 DR. McCULLEY: I based my review on what was
22 provided to me in writing, and I made no adjustments in my
23 review based on what was said today.

24 DR. WILKINSON: Well, I would hope the panel

1 can come to a decision, but what Dr. Rosenthal stated I
2 trust is obvious to us all, that these discrepancies do
3 need to be resolved, and I'm sure they will be so resolved.

4 Okay. Who on the panel would like to discuss
5 the PMA?

6 DR. BULLIMORE: I'd like to sort of request
7 some clarification on a technical issue, first of all. I'd
8 like to compliment VISX on the amount of data they
9 presented the panel with and openly acknowledge that this
10 is a much more complicated beast that we have to deal with
11 here than simple spherical myopic correction.

12 My questions really pertain to the sort of
13 ablation profile and diameter of the major and minor axis
14 of the astigmatism correction. We've already had it
15 pointed out to us that the ablations on diameter of the
16 major axis is 6 millimeters and that the minor axis can be
17 as low as 4.2 millimeters.

18 I've sort of looked at this long and hard, and
19 want to be basically sure I've got it right. The shape of
20 the ellipse -- i.e., the diameter of the minor axis -- does
21 not depend on the absolute level of astigmatic correction
22 but more the ratio of the spherical correction and the
23 cylinder correction. Is that correct?

24 ~~DR. WILKINSON: If we could have some industry~~

1 reps, and please identify yourself before speaking each
2 time.

3 DR. STEVENS: I'm Julian Stevens from
4 Moorfields in London. The geometry of the ablation zone is
5 a fixed geometry, and it depends on the ratio of the
6 sphere-to-cylinder treated. It's a relatively simple
7 calculation in terms of that geometry.

8 When a patient is treated, then that geometry
9 is fixed when it is ablated into the cornea. So
10 effectively if the sphere is correct on the long meridian,
11 you can imagine that actually the cylinder must also be
12 correct, and if there's regression in one component,
13 there's usually regression in the other.

14 DR. BULLIMORE: We can address regression and
15 efficacy. I'm just trying to get the geometry right and to
16 move on from there. So basically your answer to my
17 question was yes, it's the ratio of spherical correction to
18 cylindrical correction that determines that the profile of
19 that elliptical --

20 DR. STEVENS: Exactly.

21 DR. BULLIMORE: So if you have a -- excuse me
22 for working in minus cylinder form, but obviously that's
23 intuitive for this example. If you have a patient who is a
24 1 sphere with a 1 cyl, then you would have a profile with

1 a 6 millimeter major axis and a 4.24 minor axis.

2 DR. STEVENS: That's correct.

3 DR. BULLIMORE: And if the cylinder in that
4 example was less, obviously the minor axis would be longer.

5 DR. STEVENS: Correct.

6 DR. BULLIMORE: So in essence, rather than
7 considering the absolute level of astigmatism, one could
8 consider, as you've just pointed out, the ratio of sphere
9 and cyl in addressing safety and indeed efficacy issues
10 related to this 4 millimeter or 4.2 millimeter ablation
11 zone, which is used here.

12 DR. STEVENS: What you're suggesting is locking
13 the minor axis to a certain point.

14 DR. BULLIMORE: I'm not suggesting that we do
15 that, but that's one approach one could take.

16 One thing that you didn't cover in your
17 presentation, which I'm curious about. With that minor
18 axis being, if you like, minimized at 4.24 millimeters, in
19 instances where the cylindrical component exceeds the
20 spherical component, one then has to do an additional
21 ablation. Is that true?

22 DR. STEVENS: If you wish to exceed that ratio,
23 then you will need an additional astigmatic ablation,
24 that's quite right.

1 DR. BULLIMORE: So let's now take another
2 hypothetical example. Let's suppose that we have a patient
3 with a -1 spherical correction and a -2 diopter cylinder
4 correction. Let me see if I get it right, and you can just
5 say yes or no. If you would first do the elliptical
6 correction, which would be a -1 sphere and a -1 cyl, which
7 would have the aforementioned shape, 6 millimeters by 4.24
8 millimeters, you would then attempt to correct the
9 additional diopter astigmatism. You would then superimpose
10 thereon a cylindrical correction, which would have a major
11 axis of 6 millimeters and a minor axis of 4.5 millimeters
12 with a diopter correction, correct?

13 DR. STEVENS: A plano cylinder.

14 DR. BULLIMORE: A plano cylinder.

15 Now, in the elliptical component of the
16 ablation, you end up with a very similar profile, as you
17 said yourself, to the spherical correction where you have a
18 nice gradual transition from nonablated cornea to ablated
19 cornea. There's no sort of steep cliffs, correct?

20 DR. STEVENS: That's right.

21 DR. BULLIMORE: But in the cylindrical
22 component, you end up with a steep cliff.

23 DR. STEVENS: There is an edge blend applied to
24 that in the algorithm.

1 DR. BULLIMORE: There is an edge blend. So,
2 for example, in one of your patients presented to the
3 panel, you have a patient who is basically a plano sphere
4 with a -3 diopter cylinder, so they would have a 6-by-4.5
5 cylindrical correction only, and along one end you've got a
6 smooth ablation and the other you've got this cliff, which
7 you're telling us is later blended? What's the protocol?
8 Because that was not clear from what I read.

9 DR. STEVENS: When the parallel blades --
10 basically what happens in this situation is that the
11 parallel blades, if you can imagine them just opening up in
12 one meridian only, and to ablate the edges basically those
13 blades are just dithered at the end of the treatment and
14 that effectually smoothes the edges.

15 You can think of the plano cylindrical
16 treatment almost as an extreme form of the ellipse, with
17 one meridian of infinity, effectively. I mean, that's an
18 extreme example.

19 DR. BULLIMORE: So rather than having a sort of
20 an abrupt transition, you dither it.

21 DR. STEVENS: Yes.

22 DR. BULLIMORE: What sort of distance is the
23 blade dithered? I mean, what's the sort of nature of that
24 dithering?

1 DR. STEVENS: Well, I'm not aware of that
2 information as a user.

3 DR. BULLIMORE: Somebody's jumping up behind
4 you, eager to --

5 DR. STEVENS: I hear a whisper it's
6 proprietary.

7 (Laughter.)

8 DR. ODRICH: There is an edge calculation --

9 DR. WILKINSON: Please identify yourself.

10 DR. ODRICH: Marc Odrich, medical monitor for
11 VISX. There is an edge, a theta calculation, and we'll be
12 happy to supply it. We're not prepared at this time to go
13 into the exact dithering of how many steps.

14 DR. BULLIMORE: So you want to dither over the
15 dithering, basically.

16 DR. ODRICH: No, I don't want to dither. I
17 will mention that characterizing it as a cliff is
18 unappreciated by the epithelium, and since if you go ahead
19 and look at the epithelialization and things like that,
20 that's a concern. So I think that to say that it is cliff-
21 like is somewhat extreme.

22 It certainly is slightly less dithered than a
23 pure ellipse. However, it is a smooth transition and a
24 gradation thereof. So rather than characterize this as a

1 fall into a precipice or an endless abyss, I think we're
2 really looking at just a very smooth transition zone.

3 I'd like also to point out that that 4.5 effect
4 on the optical zone is 20 percent of a "normal" pupil. The
5 majority of the lens formed will be at the 6 millimeter
6 optical zone, and we can also go through that, too. But we
7 start getting theta and beta and I get confused up there.

8 DR. BULLIMORE: Well, I appreciate the
9 clarification, and I apologize if you found my
10 characterization offensive.

11 DR. ODRICH: No, no, not at all. I just wanted
12 to make sure from the general perspective, it is not a
13 cliff in structure. Actually, that one slide we had which
14 had the toris to show, it is unfortunate when you look at
15 these things in a cross-aspect ratio, and we did it in our
16 own PMA and we tried to, in a word, have it slope.

17 I'm not very good in word and I can't get it to
18 slope adequately, and, in fact, I know exactly the diagram
19 you're referring to, where it's at a right angle, and in
20 fact that's just inaccurate. That's why this toris was
21 shown, to try to show that this is a smooth profile.

22 DR BULLIMORE: I have no further questions at
23 this time.

24 DR. WILKINSON: Okay. Dr. Mannis?

1 DR. MANNIS: I would like to compliment VISX on
2 the presentation of the data, and particularly Dr. Eydelman
3 for an extraordinarily incisive distillation of that.

4 I don't want to carp on data today,
5 particularly, but I am concerned that at the final visit
6 our initial cohort of 116 is diminished to 84, and in the
7 diagrams that are presented we are told that 7 percent were
8 retreated, 11 percent withdrew, 6 percent missed a visit.

9 When we can change statistics from 8.7 percent
10 of patients who had greater than two lines or more of best
11 spectacle corrected visual acuity loss by explaining away
12 two or three patients, the missing 32 patients in that
13 final visit could make an enormous difference in the
14 interpretation of this data.

15 So I'd appreciate a response either from the
16 sponsor or from Dr. Eydelman as to how we interpret this
17 data based on the fact that 32 of the initial patients were
18 not present at the final accounting.

19 DR. ODRICH: Marc Odrich again. Dr. Eydelman
20 pointed to me, so I will respond.

21 The accountability table, which you will find,
22 I think, is in the early part of the document, goes through
23 the patients who were eligible versus enrolled. An

24 eligible patient for a visit is a patient who it's Table

1 7 of your document. If it's clarified, I hope maybe we can
2 take a look at it and just go through.

3 The column, the shaded column at 6, 12, and
4 final visit are the 133 eyes. Those eyes are not part of
5 the discussion that we talked about, and I believe, if my
6 math is right, the 32 is the number of eyes that you feel
7 were taken out of the study, and those should be accounted
8 for if you go to the very last column and you see that
9 eight patients were retreated.

10 Now, when this protocol and this analysis is
11 performed, retreatments are considered treatment failures.
12 That may not be the standard today by which we judge
13 refractive surgery, but from the statistical analysis
14 endpoint, those are taken out of the analysis and analyzed
15 separately. So those eight patients are retreated.
16 Unfortunately, they're under the dropout title and I
17 understand they are not dropped out. They have been
18 followed and they were presented, I believe.

19 The withdrew patients. These patients are
20 patients who are contacted by their physicians, and asked
21 to return for visits. When they don't return, they are
22 sent registered mail letters and asked to please return.
23 When that doesn't happen, the study coordinator, who is at
24 VISX, then gets involved trying to send more mail to get

1 these people in. Eventually, most of them say, sign a
2 letter and say we're not interested in returning. That
3 would be the people who withdrew.

4 You'll notice also that one patient in the 133
5 had an AK, but that did not apply to the 116, so those
6 patients come out. So of the 32 eyes that we just
7 mentioned that were not available, 13 and 8, or 21, I
8 believe have reasons statistically or in fact personally
9 for not being included and affect our analysis.

10 Not yet due for exam, we have four. So then
11 you go through getting the 21 to 25, so 25 of those 32 I
12 think we've explained. Then not examined, those are the
13 patients whose exam points are missing, for a total of
14 seven more. That gets us to those 32 eyes.

15 Certainly, I can tell you we tried everything
16 we could to get patients back in. We tried everything, and
17 we're perfectly happy to include the retreatments, but I
18 think you'll see that the retreatments at the time this
19 study was done -- the study wasn't done now. It was done
20 in 1992, and so they were handled that way. The
21 retreatments were felt to be treatment failures. This is
22 the largest group except for those that we just cannot, but
23 for love or money, get back in.

24 I hope that answers. This is not an attempt to

1 say we don't have patients or we're hiding patients. All
2 those patients with retreatments, we went back, we pulled
3 in, we tried to get everything we could for it.

4 You made another comment regarding the, I
5 believe, 8 percent, which I think is referenced to the best
6 spectacle corrected at loss. The best spectacle corrected
7 loss has three patients in a small series -- three eyes,
8 I'm sorry. Three eyes in two patients that have non-
9 corneal reasons for best spectacle loss.

10 We are not trying to say to you that they
11 aren't losses, but we are trying to say that those patients
12 were admitted into this study, for whatever reason that we
13 can discuss right now, that probably would not be admitted
14 today, but they were performed astigmatic treatments on,
15 they have to be accounted for, and we've accounted for
16 them.

17 I feel uncomfortable to present to this panel
18 that their losses of acuity were due to a corneal
19 treatment. We've done everything we can, contacted
20 investigators and said, what do you feel the reason for
21 this loss is? And when they write back to us in writing,
22 this is the increasing lens opacity.

23 I feel obligated to report that. It's not an
24 intent to say to you those losses aren't there, but it is

1 to try to link to the laser what we feel is directly
2 attributable.

3 There's one other point. There are two eyes in
4 there that we pointed out at some point had a loss of
5 220/40 or worse that we can find no reason for whatsoever.
6 That means that we did videokeratography on them, we tried
7 everything we could, including finding the investigators,
8 asking them please write, explain, call the patient back
9 in. We can't find a reason for their loss.

10 So I think there was no attempt made to try and
11 hide the accountability or eligibility of any patient, and
12 a herculean effort was made to try and get these patients
13 back in. In many instances, including a staff of three or
14 four to try and call these patients and get the registered
15 letters.

16 I hope that answers the question.

17 DR. WILKINSON: Thank you.

18 DR. ODRICH: Thank you, Malvina.

19 DR. WILKINSON: Let me just digress for a
20 moment. See, I may be responsible for the mispronunciation
21 of Dr. Eydelman's name. It is Eydelman. I apologize.
22 She's done a beautiful job not only today, but yesterday, a
23 tremendous review. So I apologize for the
24 mispronunciation. It's Eydelman.

1 Our next question will be by Dr. Higginbotham.

2 DR. HIGGINBOTHAM: Just as a follow-up to your
3 comment, was there any attempt on the part of the
4 coordinator, when he or she called the patients that didn't
5 want to come in, to assess whether or not there were some
6 subjective problems related to the procedure? For
7 instance, they didn't come in because they were unhappy, et
8 cetera?

9 DR. ODRICH: I asked our head of clinical if we
10 asked, are you dissatisfied or anything. She said
11 generally it was for things like they had moved and they
12 were uncontactable. We would return, routinely try and get
13 through to them, or they just were not interested in
14 returning. There was no more information available other
15 than that.

16 There is one other point. Dr. McCulley asked a
17 question regarding the visual function and night vision,
18 and saying that difficulty with night vision doesn't really
19 answer that question of function. I'd like to point out
20 just two things about that.

21 Difficulty with night vision was reported, and
22 it's Table 27, which has the laundry list of adverse events
23 that we reported, and you'll notice that the one column
24 missing in that table, which if I had to do PRK again I

1 would put in, is the pre-op incidence. The pre-op
2 incidence was 36 percent of the patients saying that they
3 had, and we'll be happy to supply that.

4 However, what I have asked the statistician who
5 is with us, Dr. Dumond, to do is to quickly take patient
6 assessment and do an analysis of those patients'
7 satisfaction levels. Because although functionally we
8 didn't ask that question, I think it's reasonable to assume
9 that a dysfunctional patient will be highly dissatisfied, I
10 would hope.

11 Now, if we can accept a little of that jump or
12 not, maybe we can discuss, but it's the only thing I have
13 to offer. I'd like to just say that there is a correlation
14 coefficient of 1.826 percent, and that there is a weak
15 positive relationship in the sense that as satisfaction
16 increases, night vision decreases. Complaint of night
17 vision decreases. So as satisfaction increases, complaint
18 of night vision difficulties decrease. That doesn't answer
19 the question of function, but it gives you a sense that
20 there's a very weak link, and possibly that the question is
21 not really answering.

22 Thank you.

23 DR. WILKINSON: Dr. Ferris?

24 DR. FERRIS: I'd like to follow up on the issue

1 of losses to follow-up, because from an epidemiological
2 point of view, especially when you're looking at infrequent
3 side effects, that's of great concern. I think that in
4 general the study should be congratulated for its attempts
5 at good follow-up. It must be particularly difficult to
6 follow up patients who aren't sick and getting them to come
7 back in is a lot more difficult than getting back people
8 who have a perceived problem. We have evidence that's been
9 presented that most of these people following treatment
10 don't perceive themselves to have a problem. The vast
11 majority have very high satisfaction scores.

12 Our concern, however, is at the other end of
13 the spectrum. The concern has been in the guidance and
14 other places at fairly low levels of problems that we would
15 have more concern. For example, 5 percent, 1 percent. I
16 guess at the final visit, 20 of 116 patients we don't have
17 information on. That's a modest percentage. That's 15 or
18 16 percent. The concern would be if there is some
19 disproportion in that. If that 16 percent is
20 representative of the entire group, then the proportions
21 calculated are not going to be different.

22 There was one flag that I saw that gave me some
23 concern, and that is that I believe someone presented data
24 that showed that at the final visit or at the two year

1 visit the number or the proportion of patients who had low
2 satisfaction scores went down. I believe that's true.

3
4 Whether it's true or not, it seems to me that
5 some analysis, looking at the losses to follow-up by their
6 satisfaction score when you had it before they were lost to
7 follow-up, might be worthwhile to either satisfy us that we
8 don't have a problem or to raise a flag that there may be a
9 problem of disproportionate follow-up in those who were
10 dissatisfied.

11 The question is, it's always hard to deal with
12 data that you don't have, but one of the ways of dealing
13 with it is to try to see whether there's some difference in
14 the group that you don't have from the group that you do,
15 and if those that were dissatisfied early on didn't come
16 back later, it would be worth looking at.

17 DR. WILKINSON: So the old worst case analysis
18 we used to do, could you go back to the last exam prior to
19 loss to follow-up and assess their satisfactions at that?

20 DR. ODRICH: I have two comments, and of course
21 we'll do it, gladly, but I'd like to point out, relevant at
22 the very top of this two things. The questionnaire is
23 administered, I believe, at 6, 12, and 24, is that correct?

24 Or is it just 12 and 24? Six, 12, and 24. So certainly,

1 we'll go back to the immediate previous one, but if it's a
2 24 month that's missing, we won't have an 18 month in
3 there, so that's one. We're happy to do that.

4 Generally, the recommendation at the time of
5 the panel before, and in the guidance document, is for
6 about six months of follow-up, so the questionnaires you're
7 seeing are presented over 6, 12, and final visit. But I
8 will try and have for you an answer regarding the specific
9 patients who were not seen at the final visit and what
10 their mean satisfaction level was, and if it's any
11 different from the group. So effectively, a withdrawal
12 analysis of those patient lost.

13 DR. FERRIS: One other way of looking at it
14 might be if you took the cohort that had poor satisfaction
15 scores at six months, scores of -- I forget how they're
16 rated.

17 DR. ODRICH: One through 10, and the mean at 12
18 months was 8.5, and decreasing to a mean of 8.3 at final
19 visit, which is 24 month, and 6 month would be, I believe,
20 8.4. So 8.4, 8.5, 8.3.

21 DR. FERRIS: I understand what the means are.
22 I'm worried about the ones that had scores of 1, 2, 3, or 4
23 at six months. What was their proportion of follow-up
24 compared to the proportion of follow up who had scores

1 greater than four? That's sort of an easy thing to do.
2 The numbers get pretty small because there weren't very
3 many with scores of --

4 DR. ODRICH: Well, maybe we can just quantify.
5 You're looking for four or less? We're happy to do it, but
6 just --

7 DR. FERRIS: Just trolling through the data,
8 the sample size is such an obvious problem, and right here
9 at the table figuring out how many people have less than
10 four at six months, or less than five at six months, for
11 sample size reasons you may have to go up to five or six.

12 DR. ODRICH: We could probably figure it out
13 very easily from the standard deviation. I think the
14 standard deviation on the satisfaction score, going two
15 above and two below, will tell you that you had less than
16 2.5 percent at either end, assuming a normal distribution.

17 So if we just look at that table, and could I
18 have the satisfaction table on the computer? I could give
19 you the standard deviation.

20 DR. BULLIMORE: Can you give the table number?

21 PARTICIPANT: Table 32.

22 DR. DRUM: This is Bruce Drum, FDA.

23 At six months, there are eight subjects with a
24 score of four or less. At 12 months, there are seven

1 subjects with four or less, and at final visit there are
2 three subjects.

3 DR. EYDELMAN: That's percentage-wise, however.

4 DR. DRUM: Yes, the denominator changes.

5 DR. EYDELMAN: Percentage-wise, at six months
6 it's 8.9 percent. At 12 months, it's 8.7 percent, and at
7 final visit it will be 4.4.

8 DR. WILKINSON: That's not what you wanted, is
9 it, Rick? Don't you want to know what happened to those
10 people at six months?

11 DR. FERRIS: One of the ways I would look at
12 this is, there were eight patients at six months, eight out
13 of 90, who were dissatisfied, and there were two out of 67
14 at the final visit. Now, there are two explanations for
15 that, and you can't tell from this table which is true. It
16 could be that they disproportionately drop out, or it could
17 be that they became satisfied. One of the ways to find
18 that out is to make sure they didn't disproportionately
19 drop out, and that I think you can do.

20 DR. ODRICH: One of the most common causes for
21 dissatisfaction is undercorrection, and that comes back
22 from PRK, moving forward.

23 DR. FERRIS: Of course.

24 DR. ODRICH: So knowing that if you look

1 already at the subgroup that was undercorrected, so unhappy
2 that in fact they sought retreatment and you saw how they
3 did, I would suspect that it's exactly what you just said.

4 DR. FERRIS: I suspected it, too. I actually
5 think when you do the analysis, it will strengthen your
6 situation, not the other way around.

7 DR. ODRICH: Sure, and we'll do that.

8 DR. FERRIS: But it would be an easy thing to
9 do and you can do it.

10 I would say the same thing for one other piece
11 of data that I saw that was of some concern. That is that
12 it seemed that the amount of corrections, the amount of
13 correction that was needed during follow-up to get back to
14 plano, seemed to be increasing with time, at least in one
15 of the analyses that I saw.

16 But it wasn't a cohort analysis. It was a
17 patient analysis. One of the ways of sorting out whether
18 this is a cohort effect that the early patients, for
19 example, were less well corrected, or is it a treatment
20 problem, is that there will be some drift of correction
21 over time. That could also be addressed by taking those
22 patients for whom you have follow-up over the whole time.

23 I like the analysis you did. I'm just saying,
24 do another analysis of the cohort that you had all the data

1 on to see if there was that same trend toward --

2 DR. ODRICH: Right, so you would say take the
3 84 and follow them straight through, and we did that and
4 there's no statistically significant difference.

5 DR. FERRIS: Well, statistically significant
6 difference here has its own problems because of the N, but
7 I'd just be interested in whether the trend disappeared.

8 DR. ODRICH: That would be looking at it from a
9 spherical equivalent point of view, or looking at it from
10 just a purely cylindrical point of view. That should be
11 presented in the 84 group, the Figures 1 and 2, for just
12 84.

13 We did supply an analysis of just those 84, and
14 if you look at just those 84 then you would have just the
15 84 figure in Figures 1 and 2, and that would supply you a
16 spherical equivalent and an astigmatism reduction. I mean,
17 you're right, 84 is not 116, but it's not really different.

18 DR. BULLIMORE: I'd like to follow up on some
19 of the night vision data that's been presented. I found it
20 somewhat compelling that when you look at the prevalence of
21 night vision difficulties in the post-op period, they are
22 alarming, but when you compare them to the pre-operative
23 data they seem very similar.

24 ~~What remains, though, is the stark contrast~~

1 with this new astigmatism data compared to the previously
2 approved protocol for low to moderate myopia. So my
3 question is this. I have two questions.

4 First of all, were these difficulty with night
5 vision questions collected on a prospective basis or
6 retrospective basis? That's my first question. And what
7 was the pre-operative night vision difficulties in the low
8 to moderate myopia group? Was that also at the 30 percent
9 level, or do you not have access to that?

10 DR. ODRICH: No, it was not at the 30 percent
11 level. It was significantly less, but the slide that Dr.
12 Stevens showed, demonstrating that there is no point focus
13 for these patients with astigmatism, and that our
14 correction of it is imperfect compared to a purely
15 spherical error.

16 DR. BULLIMORE: So you're suggesting that the
17 higher prevalence of difficulty with near vision --

18 DR. ODRICH: With night vision.

19 DR. BULLIMORE: Difficulty with night vision,
20 beg your pardon. Is due to uncorrected or imperfectly
21 corrected astigmatism by contact lenses, spectacles --

22 DR. ODRICH: By the three different ways we
23 said, which are in fact imperfect optical corrections, and
24 only at best approximations. That's what I am suggesting

1 to you, and that these patients are in fact perceiving this
2 differently from our myopic population. This was a
3 prospective questionnaire.

4 DR. BULLIMORE: Thank you.

5 DR. DRUM: Bruce Drum, FDA.

6 I'd like to have a clarification of these
7 percentages of night vision problems. You've been saying
8 that the percentage of people reporting night vision
9 problems is less post-op than pre-op, but in your Table 27
10 of adverse events, those night vision problem percentages
11 are specifically those who considered their night vision to
12 be worse post-op than pre-op.

13 Could you clarify that, please?

14 DR. ODRICH: Table 27 is on page 31. If we
15 look at it, Table 27 has eight categories listed, and
16 you'll note that the indented ones are under worsening of
17 patient symptoms. We do not say that that is worsening of
18 difficulty with night vision. We say that's incidence of
19 report of difficulty with night vision.

20 DR. DRUM: I'm talking about the footnote
21 that's indicated below, referring to the difficulty with
22 night vision.

23 DR. ODRICH: That is incorrect if that is said.

24 We looked at the incidence specifically across the board.

1 It is difficulty with night vision as an incidence. We'll
2 doublecheck that for you, but if that says that, that's
3 incorrect. That's taken back from the PRK table. That may
4 be why it's there. It's the incidence that we're
5 reporting.

6 We'll be happy to go back and check the
7 absolute raw numbers and give them to you.

8 DR. WILKINSON: Dr. Rosenthal?

9 DR. ROSENTHAL: I'd like to thank Professor
10 Jackson and Mr. Stevens for their excellent presentation.
11 I would like to hear from them, since I believe the major
12 issue relating to refractive surgery is proper counseling
13 of the patient. I'd like to hear what they tell these
14 patients who are having astigmatic correction with regard
15 to the possible problems and the prevalence of those
16 problems.

17 I know in the U.K. it's not as litigious a
18 society as is North America, so maybe Mr. Stevens doesn't
19 -- when I was there I never spoke to my patients anyway
20 because we never had time. We were seeing too many
21 patients. But I'm sure he had to speak to them if he's
22 correcting their vision. I'm particularly interested in
23 Professor Jackson's extensive experience in the way in
24 which the North American patients are appropriately

1 counseled, since, as I understand it, many of them have
2 crossed the border from this country to have the procedure
3 performed.

4 DR. STEVENS: Julian Stevens. I think you're
5 quite right to highlight the issue of counseling of
6 patients because a patient that has realistic expectations,
7 realistic to the outcomes that we can offer these patients,
8 will in the end be a satisfied patient in achieving those
9 expectations.

10 Patients' information in the U.K. has changed
11 dramatically since 1993, when we began the prospective
12 study, the data of which is being presented today. The
13 Royal College of Ophthalmologists in the U.K. made specific
14 recommendations to both practitioners and to patients as to
15 a standard of information for both PRK for myopia and also
16 for compound myopic astigmatism.

17 The Royal College issued a draft document in
18 1994, which became public in 1995 and is now to be revised,
19 and will be released soon in 1997. Patients are
20 encouraged, and all treating centers in the U.K. are
21 encouraged, to use the standard Royal College guidelines
22 for patients. This is independent information for
23 patients.

24 ~~Beyond that, many centers have a super set of~~

1 information they give to patients. We make sure all
2 patients have their consent forms well in advance of
3 surgery so they have plenty of time to elucidate any
4 questions. In terms of specifically for astigmatism, any
5 extra information, the only thing that we do in addition is
6 that we do look at pupil size. We do treat patients from
7 21 years onwards, but that is specifically when we have
8 documentation of a stable refraction.

9 The information for these patients contains
10 information about glare, about halos, not driving issues,
11 and so forth, but in general, for the treatment of
12 astigmatism, we haven't found it necessary to alter our
13 practice beyond the treatment of myopia. The reason for
14 that is that part and parcel of the astigmatic treatment is
15 that we are treating astigmatism for all levels, even half
16 diopter and three-quarters of a diopter, because we simply
17 program in the refraction into the machine.

18 Only about 14 percent of patients have
19 absolutely no refractive astigmatism at all. We feel that
20 the attempt to give the patient the best possible optics is
21 the aim both for the patient and for the practitioner, and
22 in the end ends with the most satisfaction. We feel that
23 is the best practice in the U.K.

24 DR. JACKSON: I would really agree with what

1 Dr. Stevens said. In Canada, I must confess that we have
2 not put any extra cautions towards the patient for the
3 treatment of astigmatism. It's now just part of the
4 routine for us. We do, though, caution patients who have
5 large pupils, and that is the one thing that we're
6 concerned about. We have still gone ahead and treated
7 those, and whether we've sensitized them to the point that
8 they're going to be delighted with the result anyway, this
9 has seemingly not been a problem.

10 I would certainly agree that in our experience
11 a number of patients coming in pre-op who are contact lens
12 wearers, who talk about problems with night vision and
13 glare, and compare that to post-operatively is very
14 similar. In fact, there are some patients who say that
15 when you're out a year or after, their night vision is
16 better after they've had the surgery than with the contact
17 lens.

18 For us also, we have rarely gone below age 21
19 and again, that's been more a stability issue in the
20 refraction rather than related to pupil size.

21 Medically and legally, in Canada there are a
22 number of cases that are going to go before the courts, but
23 in fact none relate to these issues. They're all really
24 relating to actually the practice of medicine, follow up on

1 patients, this sort of thing.

2 DR. ROSENTHAL: Thank you very much.

3 DR. WILKINSON: Thank you.

4 Other panel comments? Yes, Dr. Soni?

5 DR. SONI: I have a question about the axis
6 shift, especially the axis shift of 30 degrees in 15
7 percent of the subjects in the three-quarters to 1 diopter
8 category.

9 We all know that it's really difficult to
10 pinpoint both the axis and power of a cylinder when it's
11 less than 1 diopter. It's easier when it's 2 or 3
12 diopters. Could the sponsors comment on how accurately
13 that was measured, and what procedures were used?

14 DR. STEVENS: All treatments were based on the
15 refraction and refraction has to, for astigmatism, obtain
16 two numbers, you're quite right, both magnitude and the
17 axis. In general, axis is calibrated in 5 degree steps,
18 and magnitude in quarter diopters, so they're defined
19 specific jumps, if you like.

20 With astigmatism, if you have any degree of
21 axis misalignment, even technically 1 or 2 degrees, you
22 have an instant axis shift with a resultant astigmatism.
23 But the magnitude for such small axis errors is usually
24 very, very small.

1 That is the principle of Jackson's cross-
2 cylinders, that we have the magnitude relatively close to
3 intended, and the axis shifts out by about 40 to 45
4 degrees. It's absolutely constant. Even if your axis
5 error is 10 degrees off, your resultant always remains
6 pretty much the same axis. It's the magnitude that
7 changes.

8 So if there is an axis error, primarily because
9 of refracting errors, you're quite right, the data that we
10 feed in, then the resultant we have this axis shift, as
11 you've heard about. Then we have an axis drift, until the
12 refraction stabilizes, which as you've heard is around
13 about six months.

14 The resultant cylinders after treatment,
15 they're usually very small and these very small cylinders
16 patients don't seem to appreciate. Basically, the quantum
17 change in their refraction, particularly in their sphere,
18 is such a big quantum change that effectively any small
19 residual in cylinders are actually lost in the noise of
20 that instant benefit, if you like.

21 DR. ODRICH: Marc Odrich. The technique used
22 was taken from PERK, which had an extensive document and
23 documentation, so that the PERK guidelines were taught to
24 the investigators and they were asked to follow that.

1 Secondly, cycloplegia was used in over 90
2 percent of these patients. I believe there are two, three,
3 or four -- I can't remember the number, and we'll try and
4 get it if you're interested -- where cycloplegia was not
5 obtained. However, we did not adjust any of the treatments
6 based on either videokeratographic information, nor did we
7 adjust any of the treatments based on cycloplegia unless
8 the physician asked us to decrease the amount.

9 However, we would have had that reflected in
10 the intended, and this is always looking at intended. Of
11 the 116 eyes that were treated, and I've gone through
12 several cohorts, but I believe it's in there, that it's 20
13 or 22 eyes that were aimed at undercorrection, and it was
14 33 of the older cohort of 133 eyes. So there was a small
15 undercorrection aimed at, but the vector analysis was meant
16 to show that, and we did not adjust the reductions in the
17 scale of quantity to do that. So that you have in effect
18 the worst case analysis of that.

19 I'll just put in an aside that I think that all
20 doctors were impressed with the difficulty they have in
21 refracting cylinder generally, as compared to their
22 spherical treatments and the ease with which they were able
23 to do that, so that we have much greater respect for the
24 error of measurement of cylinder, and that is going to be,

1 I am sure, a major focus of our training that, to
2 paraphrase, garbage in, garbage out. You must take the
3 time to refract adequately, and we stress that to every
4 investigator and they were very diligent in doing that.

5 DR. WILKINSON: Thank you.

6 DR. SONI: I'll just make a follow-up comment.
7 I believe that's where I would have a question with regards
8 to correcting under 1 diopter of myopia, and unless we can
9 get to a point where we have very good methodology in
10 determining the cyl and the axis for under 1 diopter, I
11 would have a problem agreeing with that particular concept.

12 DR. BULLIMORE: I'm not going to disagree with
13 Dr. Soni, being a fellow optometrist on the panel, and
14 here's why. I see no need to place a lower limit on
15 approval for astigmatism because, yes, I will acknowledge
16 that chasing quarter or half diopter cyls round and round
17 and round is a common summertime pursuit for many of us.
18 But whereas the accuracy may be perceived to sort of be
19 less than optimal, the downside is considerably less, but
20 since you're only attempting an ablation which is designed
21 to correct an amount of astigmatism commensurate with that.

22 When you look at accuracy of refraction in
23 traditional terms, looking at cylinder axis, indeed you
24 find that the repeatability of axis determination is

1 strongly related to the magnitude of the cylinder power.
2 It's intuitive. However, when you utilize some of the
3 analysis techniques which are advocated by myself and Dr.
4 Stevens from Moorfields, using a vector approach, you find
5 that there is no such effect and basically your ability to
6 measure astigmatism is equivalent to your ability to
7 measure sphere when you think about refractive corrections
8 in this sort of vector domain that we're now being asked to
9 sort of interpret.

10 So that's my current feeling on the topic.

11 DR. STEVENS: I absolutely agree in that it's
12 well published that the standard deviation of the accuracy
13 of refraction, both the sphere, cylindrical magnitude, and
14 axis, has been documented. It's smaller for post-
15 presbyopes than for pre-presbyopes, and that demonstrates
16 that it's a subjective process, and that defines our
17 accuracy for the actual treatment procedure that we're
18 performing.

19 But there's a tremendous research interest
20 right now into refining this accuracy in terms of
21 autorefracting using the axis of that. This is a major
22 issue and I'm sure will actually be one of the key areas in
23 the future.

24 ~~DR. BULLIMORE: One issue that comes up when~~

1 you start to play around with these vectors, which really
2 places the limit in terms of the efficacy of astigmatism
3 correction, is if you're off by 30 degrees and cylinder
4 power is as intended, you basically don't reduce the power.
5 You merely shift the axis dramatically.

6 If you're off by 10 degrees, you will
7 dramatically reduce the cylinder power, but only by two-
8 thirds of the intended correction. So we've seen data here
9 in terms of absolute cylinder power reduction and you're
10 achieving about a two-thirds reduction in the U.S. data.
11 That's equivalent to being off by 10 degrees on a
12 consistent basis. Obviously, there are other factors, but
13 that's --

14 DR. STEVENS: As you saw, the magnitude error
15 of the treatments was relatively small, and that actually
16 the reason we only got a two-thirds reduction in the
17 astigmatism was primarily axis error. A 5 degree axis
18 error is a 14.7 percent undercorrection. A 10 degree axis
19 error is 34.6 percent, and you're quite right, a first
20 degree axis error is no improvement at all. You just flip
21 the axis 60 degrees.

22 DR. ODRICH: I'd also like to make the comment
23 that the multicenter study structure of the U.S. study,
24 where you saw 133 eyes spread over not just those principal

1 investigators, but spread over those principal
2 investigators and two to three subinvestigators, means that
3 you're looking really with the Moorfields and the
4 University of Ottawa with three doctors at the University
5 of Ottawa, and, Julian, how many treating doctors at
6 Moorfields? How many of them did the majority of the
7 treatments?

8 DR. STEVENS: For this particular study, three
9 surgeons did the majority of the treatment.

10 DR. ODRICH: So that in effect you're seeing a
11 difference between surgeons who have followed consecutive,
12 three surgeons having done 560 eye treatments and three
13 surgeons having performed 100, not 200, for this study, in
14 a much larger group. They are tracking their own and
15 following their own and the experience component of it
16 becomes important. I'm not suggesting that they're better
17 at refracting or they're worse at refracting, but that they
18 will be following things slightly differently.

19 DR. BULLIMORE: It would be in my experience
20 very unusual for the surgeon to actually be doing the
21 refraction on either side of the Atlantic.

22 DR. ODRICH: In the United States they are.
23 I'd like to be very clear that in the United States we have
24 forms that required sign-offs on every page, and it means

1 that that has been validated by the investigator. Not
2 necessarily that they sat there and did that, but I'm
3 saying to you that they went in there and for the most part
4 they did the refraction.

5 I can tell you, being one of the clinical sites
6 that I saw, this going on in fact. Overhead in the United
7 States being what it is, a lot of these were done by the
8 investigator. A lot of them completely done.
9 Autorefractions were not acceptable. We told them that.
10 They were not used. We never saw them. We did not want
11 them.

12 So I would say to you that although there's
13 usually a healthy dose of cynicism, we worked very hard not
14 to have that kind of error in, so that would be my comment.

15 DR. WILKINSON: Thank you.

16 DR. VAN METER: Certainly, if this procedure is
17 approved, there's no reason to suspect a fewer number of
18 investigators, and I would expect the data to actually
19 reflect more variability than we saw in the U.S. data. If
20 approved, I don't know if you can specify how the
21 refraction is done, but I would expect an even larger
22 variability with technicians or autorefractions being used.

23 It bothers me to think that this variability of
24 ~~less than 1 diopter is going to be subject to even more~~

1 unknown and variable forces than we're seeing even in this
2 study.

3 DR. ODRICH: In our labeling, in the
4 description of the document, there's a statement of
5 refractive stability, and just as in PRK we discussed the
6 age, and it's pertinent to that, too, that we have a
7 refractively stable patient, which is specifically defined.
8 In fact, that was the first point towards getting a close
9 refraction. Patients who were contact lens wearers had, if
10 they were hard lens wearers, had three stable refractions,
11 and I believe in a month or three weeks. I'd have to go
12 back and look.

13 We have very specific labeling in PRK regarding
14 what refractive techniques are strongly recommended to be
15 used. Of course, you're right, we're not going to be there
16 for every treatment and saying, don't do that, but our
17 labeling is pretty strong for PRK and we fully anticipate
18 continuing in that tradition and stating how important that
19 is. Particularly so for astigmatism, for all the reasons
20 that have been pointed out here.

21 I agree with you. I think that in the U.S.
22 experience, the multicenter study, I'm not asking that we
23 change what we do here. I'm suggesting that what we do
24 here is probably closer to being reflective, and I'd just

1 remind you there is a 64 percent reduction, if you take the
2 scalar quantities, 50 percent at Moorfields and 80.5
3 percent up in Canada. We're right in the middle. I think
4 that that really speaks for itself in terms of just the
5 reduction in scalar quantity.

6 One last point regarding the labeling. All
7 these issues, if anyone has not read the labeling for PRK,
8 are brought up, including the glare, the contrast issues.
9 So I think that the discussion regarding labeling is very
10 well handled in terms of informed consent so that the
11 patients can get the information from their surgeons.

12 DR. McCULLEY: As a surgeon who didn't do his
13 own refractions for a couple of decades, with
14 keratorefractive surgery, I guarantee you, I do. Also, as
15 a person who has done PRK, and seen patients and their
16 level of satisfaction at three-quarters to a diopter of
17 astigmatism that's left and not reduced, they're not as
18 happy a camper. So I very much, from a practical
19 standpoint, would like to see approval, including three-
20 quarters to 1 diopter, but this also goes back to one of
21 the comments I had.

22 As a surgeon who wouldn't necessarily read the
23 labeling, I think it's important. However, if I'm forced
24 to sit through a certification course whether I like it or

1 not, I'm going to get retrained to a degree in refraction,
2 and I can guarantee you that my own perspective of this,
3 relative to refractions, which, when we were all going
4 through medical school, the downer on ophthalmologists --
5 how do you want to spend the rest of your life, and which
6 is better, one or two? -- that becomes very, very important
7 with keratorefractive surgery. I think the mindset in
8 being reappraised of the fine points of refracting will be
9 taken home in that kind of setting. I think that that
10 needs to be done, and that goes back to one of my
11 conditions, that there indeed be certification for PRKa on
12 top of PRK, and that there be some specific things, that
13 are simplistic, that are stressed in that certification
14 course.

15 DR. WILKINSON: Yes, Bruce?

16 DR. JACKSON: Just a comment is that in all the
17 cases in Ottawa, the three of us do the refractions. Every
18 patient treated has had a minimum of three refractions, and
19 in fact, we refract them prior to the surgery. I think
20 that's really important, and I couldn't agree more, all of
21 us have learned to rerefract and really don't give that to
22 anyone but ourselves. I think that's the important thing,
23 and training is key if you're going to get good success.

24 DR. WILKINSON: As a retina person, I was

1 brought up that cylinders are for sissies --

2 (Laughter.)

3 DR. WILKINSON: But I can guarantee you, I've
4 heard enough this morning, particularly in our litigious
5 climate, that if you stress with labeling and with courses
6 that this must be done, that it should be done to avoid the
7 number of unhappy patients that may arise --

8 I'm also not much of a parliamentarian. It
9 seems to me that a motion will include at least three of
10 the questions Dr. Eydelman poised, but I think so we don't
11 get bogged down in amendments, I want to discuss first of
12 all question number 5. Is 18 years of age an acceptable
13 lower limit, or would we be more comfortable with age 21,
14 or perhaps a third alternative?

15 DR. McCULLEY: I think 18 is not defensible,
16 because there's no data. There was some data
17 internationally on 21. Again, my compromise position on
18 that would be 21, with the requirement for added product
19 labeling and informed consent with information about the
20 increased risk for glare, halo, and starburst in patients
21 21 to 30.

22 DR. WILKINSON: Do any panel members object to
23 that type of modification?

24 DR. RUIZ: It seems to me like 21 would be the

1 absolute minimum.

2 DR. WILKINSON: The suggestion was 21 with
3 labeling discussing a subset of age 21 to 30.

4 DR. VAN METER: Again, the youngest patient in
5 this country treated is 24. I guess empirically it's
6 reasonable to go from 24 to 21, but there is no data below
7 the age 24.

8 DR. BULLIMORE: I assume that in some way the
9 patients recruited for the study in some way reflect the
10 demand for the procedure among different age groups, and I
11 don't think that we would either way penalize the
12 manufacturer or patients by choosing one or the other of
13 those ages.

14 DR. WILKINSON: So no one has an objection to
15 our declaring unanimous okay for Dr. McCulley's suggestion?

16 DR. BULLIMORE: What was his? His was 21?

17 DR. WILKINSON: Twenty-one with labeling
18 particular to the group 21 to age 30.

19 DR. SONI: I have a point to make. Would we
20 specify why we're saying that 21? What would the labeling
21 say? Would the labeling say that we need to look at pupil
22 diameter or some other factor?

23 DR. WILKINSON: The labeling would relate to
24 the increased incidence of known complications in younger

1 patients who have bigger pupils.

2 DR. VAN METER: I would specify three things.
3 Number one, the increased incidence of complications.
4 Number two, the potential for larger pupil size, which
5 probably should be observed more than once. Number three
6 would be the variability in refraction which often exists
7 in younger patients.

8 DR. RUIZ: What's the increased incidence of
9 complications?

10 DR. VAN METER: Probably due to a larger pupil,
11 but the --

12 DR. RUIZ: Well, yes. You're saying that
13 twice. I mean, there is no increased incidence of
14 complications.

15 DR. WILKINSON: I think the second question
16 that would not be answered in just a routine motion would
17 be the stratifications of acceptability based on the pre-op
18 cylinder. That is, do we want to limit the appropriateness
19 of this device as a function of the amount of cylinder?

20 Would anyone like to speak to that question?

21 DR. McCULLEY: I will again. I reach
22 reasonable comfort -- it's not absolute, but reasonable
23 comfort -- at both the lower and -- the issues are at the
24 lower end and the upper end. If I put all the data

1 together, then I reach reasonable comfort for -0.75 to 4.

2 DR. VAN METER: The problem that I see with the
3 lower end is that really it's harder to judge the amount
4 the amount of cylinder and it's harder to judge the axis.
5 Now, maybe we're not actually really harming these
6 patients, and I would defer to your opinion, if you've
7 treated a number of patients doing refractive surgery, and
8 realize that we're not necessarily talking about patients
9 that are plano +50 or plano +25. It's more like patients
10 that are -3, -50. There's some evidence to be seen from
11 this, but again, I don't think these patients are
12 necessarily served poorly by a spherical laser ablation.

13 DR. McCULLEY: I think theoretically that is a
14 statement that certainly is very defensible, but from a
15 practical, real-world situation, these patients are not
16 happy with a residual three-quarters to 1 diopter of
17 cylinder. They're a very unhappy group. It just is not
18 going to fly. It's just not practical.

19 DR. RUIZ: Well, why do you want to limit it
20 then to 0.75 cylinder? Why not just say zero to 4?

21 DR. McCULLEY: Well, I don't want to --

22 DR. RUIZ: Which seems the thing to make sense
23 to me, because you know you're going to leave it if you
24 don't treat it. You know you're going to have a half

1 diopter, three-quarters of a diopter, if you don't treat
2 it, and if you do treat it, then you may have some
3 residual, but it's very unlikely to be that much.

4 DR. McCULLEY: Well, I'm not the one doing it.
5 They made their request, I would support their request, and
6 if they wanted to expand their request, I think that should
7 have to come from them. I'd probably want to see some
8 data, because that potentially then opens up some
9 completely new issues that we maybe haven't thought about.

10 DR. RUIZ: All the foreign data speaks to that.

11 DR. McCULLEY: We can analyze it.

12 DR. ODRICH: I'm sorry. Marc Odrich --

13 DR. WILKINSON: Let me interrupt you, Marc.

14 Dr. Rosenthal, did you have a procedural
15 question?

16 DR. ROSENTHAL: No, I just wanted to say that I
17 think the issue with the lower cyls is that it opens up a
18 Pandora's box to treat someone who is plano -0.25. You
19 know, there are very aggressive people out there who, when
20 they get their hands on this, assuming it's approved, will
21 treat --

22 DR. RUIZ: But you can leave the minimum myopic
23 restriction on there.

24 DR. ODRICH: Dr. Rosenthal, the problem has

1 been, and I think you said it, that you're always afraid of
2 a few people out there who will abuse this. However, the
3 damage to tie surgeons' hands and not allow them to make a
4 surgical judgement in the best interest of their patient I
5 think is far more detrimental than the potential.

6 Let me give you an example. For patients who
7 need retreatment, there is no basis that we have to come to
8 you and say that that should be cut off. The cards that
9 were used in this trial were cards that allowed the
10 software to be used within the recommendation that we have
11 shown for you after going back and looking.

12 However, there are retreatment cases where the
13 patients were unsatisfied. What you create is a bunch of
14 highly motivated, very angry patients, and surgeons who are
15 equally motivated and upset, because two or three or 10 or
16 100 doctors out there don't -- won't -- comply with good
17 standards of medical practice.

18 DR. WILKINSON: Thank you, Marc.

19 From a procedural issue, this is a panel
20 discussion and we can ask questions specifically of the
21 sponsor, but I think the time has passed for just comments,
22 which I allowed in error.

23 Did anyone have an additional comment?

24 DR. BULLIMORE: Personally, I'm not willing to

1 put the issue of astigmatism to bed just yet. I'd request
2 that my colleagues on the panel sort of think about it not
3 in terms of absolute value of astigmatism, but also
4 relative to the spherical power, and not in terms of an
5 efficacy issue, but in terms of a safety issue.

6 Let me compare and contrast two patients.
7 First of all, a patient who is a -1 sphere with a -1 cyl,
8 and secondly, a patient with a -3 sphere and -1 diopter
9 cyl. I'm assuming that our ability to refract those
10 patients would be equivalent and the ability to align the
11 laser or the cylinder in the phoropter or trial frame or
12 whatever would also be equivalent.

13 However, the treatment profiles of those two
14 patients would be very different. In the first patient,
15 with the -1 sphere with the -1 cylinder, they would have an
16 elliptical ablation, which would have a major axis of 6
17 millimeters and a minor axis of 4.24 millimeters. In the
18 second patient, who has a higher degree of spherical
19 myopia, they would have an ablation zone which would again
20 have a major axis of 6 millimeters, but a minor axis of 5.2
21 millimeters.

22 So to consider those two cylindrical
23 corrections as equivalent in terms of efficacy I think is
24 okay. To consider them as equivalent in terms of safety,

1 I'm not entirely comfortable with that at this moment in
2 time. You end up, due to the low spherical myopia in the
3 first patient, with a 4.2 ablation zone on the minor axis,
4 and in the second patient you have a considerably broader
5 ellipse, if you like.

6 So I'm not ready to personally vote on
7 amendments just yet. I'd like to sort of at least swirl
8 that around my own mouth a little bit more before moving
9 forward.

10 DR. WILKINSON: Well, we're going to need to
11 hear a motion. We need to know how you feel. Are you
12 voting to restrict the indications for this laser, and very
13 rigidly, apparently, based on preoperative refraction?

14 DR. BULLIMORE: At the moment, of what I've
15 heard, the motion that's been put forward has been based on
16 the degree of astigmatism, period, whether it's less than
17 -4, greater than -1. From a safety perspective, I don't
18 think you can consider it only in those ways. I think you
19 have to think about the ablation profile. I think the FDA
20 made a bold decision, and I think it was the right
21 decision, when they went with a 6 millimeter ablation zone
22 for the spherical myopia correction. I think that was a
23 good decision.

24 ~~The question is how small of an ablation zone~~

1 do we want to go to for this cylindrical correction? I
2 think that's basically the ground rule. What is the
3 minimal ablation, what's the minimum axis --

4 DR. RUIZ: Does it get smaller than 4.2, is it?

5 DR. BULLIMORE: No, that's set as a minimum.

6 DR. RUIZ: Four point four?

7 DR. BULLIMORE: It's 4.24.

8 DR. WILKINSON: That's a given. With these
9 data that are presented, it's a given that some of these
10 eyes are going to have an ablation zone of 4.24.

11 DR. BULLIMORE: Well, we have the ability
12 through amendments to raise that to a larger ablation.

13 DR. WILKINSON: That's the point. That's the
14 question I'm asking. This is not a motion. What I'm
15 trying to do is avoid a motion after the motion has been
16 made for approval, because of the parliamentary issues we
17 get into.

18 Do you feel we can assess the panel in terms of
19 does anyone feel strongly that we do need to dictate that
20 small ablation zones cannot be used, cannot be used except
21 in special circumstances, et cetera? The point is, a lot
22 of these eyes had ablations with small zones. That's in
23 the data.

24 DR. FERRIS: Have we seen the data stratified

1 by, for example, the cohort that had between 4.24 and 5?

2 DR. BULLIMORE: That's one analysis I haven't
3 seen.

4 DR. FERRIS: And double vision, sensitivity to
5 light, contrast sensitivity, night vision problems? Are
6 the differences or are these problems much greater in the
7 group with the --

8 DR. RUIZ: We don't have that information. Are
9 you uncomfortable with 4.24?

10 DR. FERRIS: I don't know how you make a
11 decision without it.

12 DR. RUIZ: You vote against 4.24 if we vote? I
13 want to hear you dilate a little bit more on your thoughts
14 here. Give us the minimum you're happy with.

15 DR. BULLIMORE: Okay. We've basically got to
16 draw a line in the sand, and 4.24 is the wrong side of the
17 line as far as I'm concerned.

18 DR. RUIZ: Give us a line.

19 DR. BULLIMORE: Well, let's say 5. Okay? This
20 is open for debate.

21 DR. RUIZ: Yes. I'm just trying to bring it to
22 focus.

23 DR. BULLIMORE: I'm just giving you my opinion,
24 and obviously, some people have a different opinion based

1 on their reaction.

2 DR. McCULLEY: I don't think this is going to
3 go anywhere that I can see. We have data, we have 4.24 as
4 the minimum, and we have not had a presentation of
5 information at all. The company has not been asked to do
6 that. I assume they don't have that off the top of their
7 head, which would take a completely different approach to
8 this whole application. I don't see the productivity in
9 going down this road. I'm sorry.

10 Now, even if it's a better road, we go down the
11 road to approval, but I don't see any good point in going
12 down this road that we're starting down, because I don't
13 think we can effectively do it, and when you're ready, I do
14 have a motion.

15 DR. WILKINSON: This might be a good time,
16 since this has to be done anyway, for Sally to read into
17 the record the options that we, as panel members, have.

18 MS. THORNTON: Reading into the record, "The
19 medical device amendments to the federal Food, Drug, and
20 Cosmetic Act require that the Food and Drug Administration
21 obtain a recommendation from an outside expert advisory
22 panel on designated medical device premarket approval
23 applications that are filed with the agency. The PMA must
24 stand on its own merits and your recommendation must be

1 supported by safety and effectiveness data in the
2 application or by applicable publicly available
3 information."

4 "Safety" is defined in the Act as "reasonable
5 assurance, based on valid scientific evidence, that the
6 probable benefits to health, under conditions of use,
7 outweigh any probable risks."

8 "Effectiveness" is defined as "reasonable
9 assurance that in a significant portion of the population,
10 the use of the device for its intended uses and conditions
11 of use, when labeled, will provide clinically significant
12 results."

13 Your recommendation options for the vote are as
14 follows. Number one, approval. There are no conditions
15 attached in that case. The agency action is, if the agency
16 agrees with the panel recommendation, an approvable letter
17 will be sent to the applicant.

18 Number two, approvable with conditions. You
19 may recommend that the PMA be found approvable subject to
20 specified conditions, such as resolution of clearly
21 identified deficiencies which have been cited by you or by
22 FDA staff.

23 Prior to voting, all of the conditions are
24 discussed by the panel and listed by the panel chair. You

1 may specify what type of follow-up to the applicant's
2 response to the conditions of your approvable
3 recommendation you want. For example, FDA or panel follow-
4 up. Panel follow-up is usually done through homework
5 assignments to the primary reviewers of the application or
6 to other specified members of the panel. A formal
7 discussion of the application at a future panel meeting is
8 not usually held.

9 If you recommend post-approval requirements to
10 be imposed as a condition of approval, then your
11 recommendation should address the following points. A, the
12 purpose of the requirement. B, the number of subjects to
13 be evaluated and the reports that should be required to be
14 submitted.

15 The agency action, for an approvable with
16 conditions recommendation, if the FDA agrees with the panel
17 recommendation, an approvable with conditions letter will
18 be sent.

19 Not approvable, of the five reasons that the
20 Act specifies for denial of approvable, the following three
21 reasons are applicable to panel deliberations. The data do
22 not provide reasonable assurance that the device is safe
23 under the conditions of use prescribed, recommended, or
24 suggested in the proposed labeling. Reasonable assurance

1 has not been given that the device is effective under the
2 conditions of use prescribed, recommended, or suggested in
3 the labeling. Based on a fair evaluation of all the
4 material facts in your discussion, you believe the proposed
5 labeling to be false or misleading. If you recommend that
6 the application is not approvable for any of these stated
7 reasons, then we ask that you identify the measures that
8 you think are necessary for the application to be placed in
9 an approvable form.

10 If FDA agrees with the panel's not approvable
11 recommendations, we will send a not approvable letter.
12 This is not a final agency action on the PMA. The
13 applicant has the opportunity to amend the PMA to supply
14 the requested information. The amended application will be
15 reviewed by the panel at a future meeting unless the panel
16 requests otherwise.

17 In rare circumstances, the panel may decide to
18 table an application. Tabling an application does not give
19 specific guidance from the panel to FDA or the applicant,
20 thereby creating ambiguity and delay in the progress of the
21 application. Therefore, we discourage tabling of an
22 application.

23 The panel should consider a not approvable or
24 ~~approvable with conditions recommendation that gives~~

1 clearly described corrective steps. If the panel does not
2 vote to table a PMA, the panel will be asked to describe
3 which information is missing and what prevents an
4 alternative recommendation.

5 Following the voting, the chair will ask each
6 panel member to present a brief statement outlining the
7 reasons for their vote.

8 Thank you, Dr. Wilkinson.

9 DR. WILKINSON: Thank you.

10 May I hear a motion?

11 DR. McCULLEY: I'll make a motion, but I'd like
12 to ask for some procedural clarification first. There were
13 three issues that I had concerns about that I would like to
14 include in some place. I'm not sure where that is, whether
15 it's in the motion and recommendation with concerns or
16 conditions, or where it would appropriately be. I'd like
17 guidance on that.

18 Those three issues related to informed consent,
19 postmarket surveillance, and necessity for surgeon
20 certification. Would those be a part of the motion, would
21 they be a motion with conditions, or would those be issues
22 that would just simply be stated after a simpler motion and
23 the FDA would take into advisement when dealing with the
24 company?

1 DR. RUIZ: Any one of the three.

2 DR. McCULLEY: All right. Which one?

3 DR. RUIZ: Pick.

4 DR. WILKINSON: Does anyone disagree with the
5 fact that those should be included?

6 PARTICIPANT: Can you summarize them again?

7 DR. McCULLEY: Yes. I'm not sure that they
8 should be conditions. They're not that strong, I don't
9 think, but again, it's a procedural question.

10 Okay. Informed consent was the first, that
11 patients be informed that there's an increased risk,
12 relative to PRK, for a loss of two lines of best spectacle
13 corrected visual acuity and that there's an increased risk
14 for glare, halo, starburst, and the associated problems
15 with that.

16 Second, that there be postmarket surveillance
17 on loss of best spectacle corrected visual acuity, increase
18 in glare, et cetera, the stability of the axis, under
19 postmarket surveillance.

20 Third, that there be the requirement for
21 surgeon certification for PRKa, in addition to the
22 previously required for PRK for those that have already
23 been certified for PRK, and that there be stress on
24 ~~necessity and accuracy of measurement of pupillary~~

1 diameter, preoperative refractive determination, and
2 necessity of and techniques for centration and axis
3 alignment.

4 DR. WILKINSON: We will recommend that you do
5 include those in your motion. You don't need to repeat
6 them, I don't believe.

7 DR. McCULLEY: Thank you.

8 MS. THORNTON: You should formulate your
9 requirements as forms of conditions of approval, and
10 please, I'd like for us to differentiate between postmarket
11 surveillance and post-approval follow-up.

12 DR. McCULLEY: Again, tell me, and I will.
13 Which one? Tell me the difference and I'll tell you which
14 one I want.

15 MS. THORNTON: Postmarket surveillance
16 involves, and I'm not altogether completely clear on this,
17 but it does involve procedures that are above and beyond
18 what we're asking the company to do now. I believe Nancy
19 or Ralph can tell you more about the regulatory formula for
20 that, but post-approval follow-up is usually to keep
21 following the patients that have been involved in the
22 studies so far.

23 DR. McCULLEY: That are already entered.

24 MS. THORNTON: Yes.

1 DR. McCULLEY: No, that's not what I'm after.

2 MS. THORNTON: I wanted you to know that, but
3 also to formulate what you think should be the conditions
4 based on your concerns.

5 DR. McCULLEY: Well, it may be that the things
6 that I had in postmarket surveillance, after the
7 discussions today, I could actually drop that whole issue
8 out, because I don't think it's as strong as I did going
9 into these discussions. I would drop mine, actually, then
10 to two, the informed consent issues and the surgeon
11 certification.

12 DR. WILKINSON: Dr. Rosenthal?

13 DR. ROSENTHAL: May I clarify? Two issues.
14 The first is your issue of informed consent. I presume
15 that relates to the information that is given in the
16 patient information booklet that is required for
17 photoablative --

18 DR. McCULLEY: Right.

19 DR. ROSENTHAL: Okay. Secondly, just to raise
20 the issue of postmarket surveillance, I don't think it is a
21 practical issue -- and this is just my own personal opinion
22 -- to ask the company to try to collect the data on axis
23 shift and losses of two lines of visual acuity from
24 practicing physicians. The regulation is that hospitals

1 and treatments facilities have to report adverse events,
2 but many of these procedures take place outside those two
3 facilities. I don't think putting that recommendation in,
4 although it would be very interesting information to have
5 and one would love to have it, I don't think you're going
6 to get any type of meaningful information.

7 DR. McCULLEY: I would accept the other opinion
8 stated relative to informed consent, with the assumption
9 that that then, in effect, is going to happen, and I will
10 back off on the postmarket surveillance for the reasons
11 that everyone can interpret what's been said.

12 That would leave me with the one condition that
13 the users receive additional certification for PRKa, and in
14 effect that PRK certification does not provide PRKa
15 certification, that there has to be additional
16 certification.

17 DR. RUIZ: Who's going to do that? The
18 company?

19 DR. McCULLEY: It would be the company, yes,
20 presumably.

21 DR. RUIZ: So you're going to make your motion?

22 DR. McCULLEY: I make a motion --

23 DR. WILKINSON: Wait. Hold on.

24 Do you have a pre-motion?

1 DR. MANNIS: Before you do, just to avoid
2 problems, are you not including in your conditions any
3 specification of the degree of astigmatic correction? I'm
4 not sure we reached a consensus on that issue, either lower
5 or upper.

6 DR. McCULLEY: I was and I thought we had.

7 DR. MANNIS: Did we?

8 DR. McCULLEY: I was going by 0.75 to 1 from a
9 practical standpoint, and given the data presented, I'm
10 perfectly comfortable with safety and efficacy, and 3 to 4,
11 I think there is enough data to give me reasonable comfort.
12 So yes, I was going to include in my motion the limits, and
13 I was not going to restrict them.

14 DR. BULLIMORE: I'm happy to consider the
15 amendment and vote upon the amendment as stated, informed
16 consent, PMS, and certification. In doing so, I assume you
17 don't close the door on the discussion of other issues,
18 such as astigmatism.

19 DR. McCULLEY: Well, PMS has already been --

20 DR. WILKINSON: It's deleted.

21 DR. ROSENTHAL: Let me clarify again. There is
22 postmarket surveillance, which I have already commented on.
23 There are postmarket studies, which you could require the
24 company to perform.

1 DR. BULLIMORE: I'm not trying to rephrase Dr.
2 McCulley's motion. It's really a question. I'm the new
3 kid on the block here. I don't understand whether, by
4 voting on these amendments, we exclude any other amendments
5 and further discussion.

6 DR. RUIZ: He hasn't made his motion yet.

7 DR. McCULLEY: Roberts will probably role over
8 in his grave. I'd be happy to put out a straw motion, and
9 we can go from there, or I can make a motion, or we can
10 keep talking around the issue.

11 DR. WILKINSON: Make the motion.

12 DR. McCULLEY: All right. I'd like to make the
13 motion that we recommend approval of this PMA as requested
14 by the sponsor, with the one exception that the lower age
15 limit be set at 21 and not 18, and with the one issue that
16 I would still leave as a requirement, and that is that
17 there be additional surgeon certification by the company
18 with appropriate education relative to PRKa.

19 DR. RUIZ: Second.

20 DR. WILKINSON: Do you want to say the company
21 has to do this? Suppose the American Academy of
22 Ophthalmology wanted to?

23 DR. McCULLEY: Well, the responsibility has to
24 be at the company, and then they can do it however they

1 want to.

2 DR. ROSENTHAL: But could we not use the word
3 "certification," but just training?

4 DR. McCULLEY: Okay, training, that there be
5 appropriate formal training of surgeons for PRKa.

6 DR. ROSENTHAL: And if I may, after you vote, I
7 would like to discuss a little bit about this issue of
8 training requirements, okay?

9 DR. McCULLEY: I accept Dr. Rosenthal's
10 friendly amendment to my motion.

11 DR. WILKINSON: It's been moved and seconded --

12 DR. McCULLEY: You probably can't do that, can
13 you?

14 DR. RUIZ: Just restate it. He's not amending
15 it. He's just telling you --

16 DR. ROSENTHAL: If no one seconds that, you can
17 then go back and redo it.

18 DR. RUIZ: Restate your motion.

19 DR. ROSENTHAL: Don't anyone second it.

20 DR. McCULLEY: Do I have to restate it?

21 DR. ROSENTHAL: You have to restate it if no
22 one seconds it, because we can't change it.

23 DR. WILKINSON: It's been seconded.

24 DR. McCULLEY: I accept that friendly

1 amendment.

2 DR. WILKINSON: It's been moved and seconded,
3 and it's open for discussion.

4 DR. MANNIS: Jim, could you go back and provide
5 for us the basis on which you feel that there is enough
6 data to accept correction above 3 diopters? I am
7 concerned, as I think Dr. Van Meter is, that there is not
8 sufficient data we are presented to correct above 3
9 diopters of astigmatism safely.

10 DR. McCULLEY: There were, I believe, six
11 patients in the U.S. study and there were something less
12 than 20 -- I try not to remember too many silly little
13 numbers. It was just less than 20. It was 17 or 18, but
14 roughly 20 patients from the U.K. with follow-up data.

15 That personally, in this setting, gives me
16 enough comfort. When you start getting into the larger
17 degrees of correction, it's hard to find large numbers.
18 There were enough there to give me reasonable comfort.
19 There were over 20 patients.

20 DR. VAN METER: In the U.S. study, there were
21 six patients treated. Three of them have 12-month data.
22 No patients have 24-month data.

23 DR. McCULLEY: I don't want to get into the
24 situation of having to defend everything, but we initially

1 said to the company, or to industry, relative to this, that
2 we would like to see -- I saw myself on TV --

3 (Laughter.)

4 DR. McCULLEY: A hundred and fifty patients
5 with six-month data. We have 6-month, 12-month, 24-month
6 data. There was enough data there to give me reasonable
7 comfort, given the realities of the situation. That's
8 where I'm coming from.

9 DR. WILKINSON: There were over 40 in the
10 Ottawa group, weren't there?

11 DR. HIGGINBOTHAM: Yes, there were 48 in the
12 Ottawa study.

13 DR. WILKINSON: I'm sorry to interrupt. It's
14 been pointed out to me that the motion is a motion to
15 approve with conditions, the conditions being the change in
16 age and the requirement for education.

17 DR. HIGGINBOTHAM: Just a point of
18 clarification. Are we backing away from the concern about
19 the 21- to 31-year-olds in terms of making sure that
20 they're informed regarding the halos because of pupil size
21 issues?

22 DR. McCULLEY: No, I don't think I really am,
23 and I guess I was just making the assumption that that
24 would still be in there in the patient information book.

1 If that needs to be more clearly stated in this forum, I'd
2 be happy to do so, but no, I didn't want to back off of
3 that.

4 DR. HIGGINBOTHAM: I think I would be more
5 comfortable if that's clearly stated in your motion.

6 DR. McCULLEY: Do I need to include that in my
7 motion?

8 DR. RUIZ: Why don't you make it as an
9 amendment, Eve?

10 DR. WILKINSON: Eve, do you want to propose
11 that as an amendment?

12 DR. HIGGINBOTHAM: So amended.

13 DR. McCULLEY: Second.

14 DR. WILKINSON: I hear a second. It's been
15 moved and seconded that the amendment regarding the
16 increased incidence of visual problem phenomena and
17 relative youth be added as requirement --

18 DR. McCULLEY: In the patient information.

19 DR. WILKINSON: In the patient information
20 publication. Any discussion on that issue?

21 (No response.)

22 DR. WILKINSON: All those in favor, signify by
23 raising their right hand.

24 (Show of hands.)

1 DR. WILKINSON: All those opposed?

2 (Show of hands.)

3 DR. BULLIMORE: What was that on?

4 DR. WILKINSON: We're voting on a motion for
5 the amendment to include in the patient information
6 brochure the fact that patients from age 21 to 30 are at
7 particular risk for visual complications.

8 DR. BULLIMORE: Are we voting on the amendment
9 or are we voting on --

10 DR. WILKINSON: We're voting on the amendment,
11 approval of the amendment as an additional condition.
12 We're voting on a proposal --

13 DR. VAN METER: Mine is a yes vote.

14 DR. WILKINSON: Okay.

15 DR. BULLIMORE: And mine is a yes vote.

16 DR. WILKINSON: So it's unanimous that that
17 condition be added. We now have three conditions, and the
18 original motion stands as a motion for approval with
19 conditions.

20 Is there further discussion of this motion?

21 (No response.)

22 DR. WILKINSON: If not, all those in favor of
23 the motion, which is a motion to approve with the
24 ~~conditions previously stated, signify by raising their~~

1 right hand.

2 (Show of hands.)

3 DR. WILKINSON: And all those opposed, signify
4 by raising their hand.

5 (Show of hands.)

6 MS. THORNTON: I have four for and three
7 against.

8 DR. WILKINSON: Four for and three against.

9 MS. THORNTON: For approval with those
10 conditions.

11 DR. RUIZ: You're not voting, Mr. Chairman?

12 MS. THORNTON: No, it's not a tie.

13 DR. WILKINSON: We now will poll the panel
14 members for their individual comments regarding their vote.
15 Dr. Van Meter, we'll start with you, and move in this
16 direction.

17 DR. VAN METER: I voted nay. I agree with all
18 of the amendments proposed. My concerns are including the
19 range of 3.1 diopters and greater with only three patients
20 in 12-month data within this country. I'm also concerned
21 about the 0.75 to 1.0 diopter range also being treated.
22 I'm essentially in agreement with everything else outside
23 those conditions.

24 MS. THORNTON: Dr. Bullimore?

1 DR. BULLIMORE: I'm in agreement with all of
2 the amendments that were put forward. I have residual
3 concern about the ablation diameter along the minor axis.

4 MS. THORNTON: And you voted nay.

5 DR. BULLIMORE: Yes, I voted no.

6 DR. McCULLEY: I made the motion. I was
7 comfortable with it. I think that I reached a reasonable
8 level of confidence in safety and efficacy, and felt from a
9 practical standpoint that my concerns that I had were dealt
10 with effectively, and that the motion as stated was
11 appropriate.

12 MS. THORNTON: Dr. Higginbotham?

13 DR. HIGGINBOTHAM: I voted in favor. I think
14 that the international data was helpful in my decision,
15 given the greater numbers of patients in the higher diopter
16 range. I think that, given the process of informed
17 consent, that patients will be able to make a reasonable
18 decision.

19 MS. THORNTON: Thank you.

20 Dr. Ruiz?

21 DR. RUIZ: I voted in favor of the motion. I
22 think that we're not living in a vacuum here. There is
23 plenty of data from Canada and from the United Kingdom that
24 we should look at and did look at. I have a reasonable

1 comfort with the request from the company and voted yes.

2 MS. THORNTON: Dr. Mannis?

3 DR. MANNIS: I voted in favor, although I still
4 have some concerns about the amount of data we have on
5 higher degrees of cylinder correction. I didn't think that
6 it mitigated a positive vote signifying reasonable safety
7 and efficacy.

8 MS. THORNTON: Thank you.

9 Dr. Soni?

10 DR. SONI: I opposed the motion on the basis of
11 the lower limit of the cyl correction. There is very
12 little data presented by the sponsor on the visual symptoms
13 broken out into the different categories of the cyl
14 correction. I am also concerned about the inadequate
15 amount of data on higher levels of cyl correction.

16 MS. THORNTON: Thank you.

17 DR. WILKINSON: We'll now have a few
18 announcements from the secretary.

19 MS. THORNTON: Thank you very much, panel, for
20 your time and your concerns and your reviews. We
21 appreciate that very much.

22 I believe Dr. Rosenthal has another comment
23 that he would like to make. I'll let him go ahead, and
24 then I'll finish up.

1 DR. ROSENTHAL: I would like the panel's
2 consideration of questions 2 and 4, which Dr. Eydelman
3 presented to the panel, in a broader context. That context
4 is the endpoints which we have discussed, particularly
5 relating to issues of adverse events. Are they appropriate
6 for all future astigmatic presentations? This has actually
7 been requested by the office director, Dr. Alpert.

8 DR. RUIZ: I don't understand the question.

9 DR. ROSENTHAL: Are the issues, which we have
10 discussed here with regard to both efficacy and safety, are
11 the numbers that we have accepted here and voted for here,
12 will they be our guideline for future submissions?

13 DR. RUIZ: Well, I mean, we haven't accepted
14 all of them. Four of us voted for it and three against it,
15 and all the ones against it were based on the astigmatism
16 situation, so I don't know if we can answer that question.

17 DR. WILKINSON: Ralph, these questions are not
18 specific to all devices. It says "of this device" in both
19 instances, so there is nothing generic or universal --

20 DR. ROSENTHAL: No, I know it's not generic,
21 but this is an issue that Dr. Alpert wanted me to raise
22 with the panel as a separate issue.

23 DR. WILKINSON: Well, as I understood the
24 presentation, there was a limit set on a 5 percent loss of

1 two lines for astigmatic PRK. That was stated only by the
2 sponsor. Is that correct? That's from the guidance
3 document.

4 DR. McCULLEY: And they came under that.

5 DR. WILKINSON: So are you referring back to
6 those criteria? Because the criteria have already been
7 established, as far as I know.

8 DR. ROSENTHAL: We're happy with the criteria
9 for future astigmatic correction.

10 DR. WILKINSON: Well, the numbers are 5
11 percent, which --

12 DR. McCULLEY: I don't think we went beyond the
13 guideline in any meaningful place. It's kind of hard -- I
14 don't like being in a box, and when you're looking at the
15 whole thing, you know, we looked at a whole application,
16 and to take one piece and say, this now is the guideline
17 for henceforth, without taking it into the bigger picture,
18 I would not be very comfortable with that.

19 DR. ROSENTHAL: There is one other thing, and
20 that is since you do have a lower limit on the astigmatism
21 that has been approved of 0.75 diopters, the agency will
22 take the tack that the labeling will have to reflect quite
23 strongly this lower limit.

24 DR. WILKINSON: Dr. Gordon?

1 DR. GORDON: I'd like to raise one last issue
2 and it was probably more appropriate earlier in the
3 discussion, but it's something that keeps coming up
4 relative to loss to follow-up and the concern that there
5 was really only a cohort of 84 patients in the U.S. study.
6 The sponsor indicated that they made repeated efforts to
7 contact the patients by registered mail. One of the things
8 we used to do in intraocular lens studies was interview the
9 patients on the phone.

10 I'd love to hear from Dr. Ferris or from anyone
11 else on the panel whether some follow-up, some contact --
12 for example, "Are you unsatisfied? Is that why you haven't
13 returned? Have you had any additional interventions? Have
14 you sought treatment from another ophthalmologist?" and
15 night driving, those kinds of things -- a questionnaire
16 could be mailed to the patient, the patient could be
17 interviewed on the phone.

18 Rick, how does that fit into this in terms of
19 providing better reassurance of more complete follow-up?
20 Because that issue comes up again and again in all of these
21 studies, and this is a very young, mobile population, and
22 it's very hard to pin them down. Again, every informed
23 consent, for every study, says the patient can exit any
24 time without any detriment to his future care. It's very

1 clear. It's a requirement.

2 I would love to hear just a little bit about
3 whether that's something sponsors ought to begin
4 considering as a means of gaining more information.

5 DR. ROSENTHAL: I have one more comment. I'm
6 sorry. I'll let you get to lunch almost immediately after
7 this.

8 There has been a major issue relating to the
9 training requirement with regard to the practicing
10 community. As you know, FDA can only regulate the
11 companies, and the requirement has been put on the
12 companies to see that the training is given to the
13 practicing physician.

14 There have been many complaints, and I'm sure
15 you're aware of them as well, from the practicing community
16 that there has been less than optimal cooperation with
17 professional organizations to provide that training, and
18 though we cannot make a requirement of you as to who does
19 the education and training, we hope you will be amenable to
20 allowing professional organizations to take on some of the
21 responsibility which the company has, so that you insure
22 that the training is provided, but not necessarily given by
23 VISX.

24 Thank you.

1 DR. McCULLEY: There has to be some assurance
2 that that training was done and it's not just that a
3 mailing was sent with "These are the things you have to be
4 concerned about with this new procedure, please sign this
5 piece of paper, and send it back indicating that you've
6 read it." I think that with a procedure such as this, and
7 the risk, that that is not sufficient.

8 DR. ROSENTHAL: Well, whatever the ultimate
9 training requirement is, we can only require the company to
10 insure that the training is given, okay? But I would want
11 the company to know, and future companies, that we feel --
12 and certainly I feel personally, not in my capacity as the
13 division director -- but I feel, and I think most of my
14 professional colleagues feel, that other people, other than
15 the exact people designated, professional organizations,
16 can take on part of these training requirements, assuming
17 that you insure that they give the information you're
18 required to insure that the people who take that course
19 get, if I'm making myself clear.

20 It has been a big problem with excimer laser
21 training and a lot of discomfort by the practicing
22 ophthalmologist. I'm sorry to raise it now, but I don't
23 know any other venue in which to raise it.

24 DR. WILKINSON: I think the beginning

1 refractive surgeon would want as much help from the company
2 as he could get.

3 Dr. Gordon did make a comment, which demanded a
4 response which has not been made. Speaking for myself, I
5 think it's very, very helpful to know that a company
6 actually made contact with a patient, that in fact the
7 patient has not failed to return because of
8 dissatisfaction. It would be even better if you could
9 document that by sending the patient a stamped self-return
10 envelope checking off a box. There's always an element of
11 trust in terms of sure, she said she was happy, and to have
12 it in writing is always helpful, but I think any way you
13 can document that patient is still on the face of the earth
14 is a good idea.

15 Would others like to comment on Dr. Gordon's
16 question before we move on?

17 DR. RUIZ: I'd just echo what you said. I
18 think it's very valuable information, whether it's gotten
19 by phone or written or whatever.

20 This is a problem, though, with all these
21 studies in the United States where there are multiple
22 investigators spread all over the place, and the follow-up
23 varies considerably. You look at the Canadian data, it had
24 100 percent follow up, because there were three of them

1 doing it, they established rapport with those patients,
2 they did their own refractions, they did their own follow-
3 up, and those patients come in.

4 When you're talking about 60 surgeons spread
5 all over the country, it doesn't work. I may be wrong
6 about this, but probably in England they're not doing any
7 of their own refractions, and that's why the correction was
8 50 percent, rather than 80.

9 DR. FERRIS: With regard to losses to follow-up
10 and what to do about it, I believe that anything that you
11 can do to close the gap between information that is best
12 and information that's absent is better. I guess one
13 thinks of a grey zone between what's acceptable in terms of
14 losses to follow-up, and data that's presented here has
15 pushed the grey zone to its limit. Not today, but in some
16 previous panel discussions, where we've had no idea what's
17 happened to large proportions of the patients. Anything
18 that can be done to give some comfort that the patients
19 that were missing were comparable to the patients that you
20 have data on, if you can have some other information,
21 that's fine.

22 The one caveat that's come up over the years
23 that I've been involved in clinical research is that you
24 have to be careful about badgering patients. I think we

1 have to recognize that not everybody is going to be willing
2 to provide even minimal information. Apparently, there is
3 even some question about mortality now, but up until now
4 we've been able to find out whether people were living or
5 dead. Hopefully, we will continue that.

6 So, as a committee or a group, we have to
7 recognize that 100 percent follow-up in this country may be
8 difficult.

9 DR. WILKINSON: Yes, Dr. Mannis?

10 DR. MANNIS: I just have a procedural question
11 for Dr. Rosenthal. Given the fact that the vote was split
12 a little bit on the issue of astigmatism, in making its
13 final ruling, will the Devices Branch further deal with the
14 issue of limits upper and lower or will that simply go
15 unmentioned in the final deliberations with the company?
16 The issue of an upper limit of 3 or a lower limit of 0.75,
17 is the issue over? That's what I'm asking.

18 DR. ROSENTHAL: The panel has made its
19 recommendation, and we have heard the objections to the
20 recommendation and the opposing views. All views will be
21 taken into consideration when a final decision is made
22 concerning the device.

23 DR. WILKINSON: Any more comments?

24 (No response.)

1 MS. THORNTON: If there is nothing further, I
2 just wanted to make a few short announcements. There is a
3 package for Dr. David Archer waiting at the registration
4 desk.

5 The remainder of the 1997 panel meetings that
6 have been tentatively scheduled are March 27th and 28th,
7 July 10th and 11th, and October 20th and 21st. Those dates
8 are on the Web page, address www.fda.gov. Changes or
9 cancellations of those dates will appear, as well as draft
10 agendas of the planned meetings. Information on the
11 planned meetings can also be obtained from the panel
12 hotline. The number is 1-800-741-8138. The Ophthalmic
13 Devices Panel code, when prompted by the recording, is
14 12396.

15 Again, I want to thank you all for your
16 attention and your attendance, and particularly for those
17 folks who have put in a lot of hard work preparing for
18 today.

19 Thank you, and we'll see you at the next
20 meeting.

21 (Whereupon, at 1:05 p.m., the meeting was
22 adjourned.)

23
24

1

2