

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

Friday,
July 11, 1997

Ballroom
Gaithersburg Hilton
620 Perry Parkway
Gaithersburg, Maryland

IN ATTENDANCE:

Voting Panel Members

JAMES P. McCULLEY, M.D., Interim Chair
MARK A. BULLIMORE, MCOptom, Ph.D.
EVE J. HIGGINBOTHAM, M.D.
MARIAN S. MACSAI, M.D.
RICHARD S. RUIZ, M.D.
PREM SARITA SONI, O.D., M.S., F.B.C.O., F.A.A.O.

Consultants, Deputized to Vote

JOEL SUGAR, M.D.
WOODFORD S. VAN METER, M.D.

Non-Voting Discussants

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

Panel Executive Secretary

SARA M. THORNTON

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Division of Ophthalmic Devices, FDA

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P R O C E E D I N G S

(8:13 a.m.)

1
2 DR. McCULLEY: This is the July 11th, 1997,
3 open session of the FDA Ophthalmic Devices Panel. I would
4 like to turn over the meeting for introductory remarks to
5 Sara Thornton.

6 MS. THORNTON: Good morning to all attendees.
7 Before we proceed with today's agenda, I have a few short
8 announcements to make.

9 During the break, you may purchase coffee, tea,
10 and pastries at the Martingayle's restaurant, which is just
11 off the lobby, if you haven't walked by there already.

12 Messages for panel members and FDA
13 participants, information, or special needs should be
14 directed through Ms. Ann Marie Williams, who is sitting on
15 the end there of the FDA section, or Ms. Christie Wyatt,
16 and she will probably be out at the table in the lobby
17 there. Give them to those two people or someone at the
18 sign-in table for help, please.

19 Will all meeting participants today please
20 speak into the microphone, so that the transcriber will
21 have an accurate recording of your comments.

22 Now, at this time, I'd like to extend a special
23 welcome and introduce Dr. Joel Sugar, who has recently
24 ~~joined the Ophthalmic Devices Advisory Committee as a~~

1 consultant. Dr. Sugar is professor of ophthalmology and
2 director of the Corneal Service at the University of
3 Illinois Eye and Ear Infirmary in Chicago, Illinois, and is
4 also the medical director of the Illinois Eye Bank.

5 Dr. Sugar, I'd like to welcome you this
6 morning.

7 DR. SUGAR: Thank you.

8 MS. THORNTON: To continue, will the remaining
9 panel members please introduce themselves, beginning with
10 Dr. Frederick Ferris?

11 DR. FERRIS: Frederick Ferris, director of the
12 Division of Biometry and Epidemiology at the National Eye
13 Institute, National Institutes of Health.

14 DR. BULLIMORE: Mark Bullimore, assistant
15 professor at the Ohio State University College of
16 Optometry.

17 DR. MACSAI: Marian Macsai, professor and
18 director of Cornea and External Disease Service, West
19 Virginia University.

20 DR. McCULLEY: Jim McCulley, professor and
21 chairman, Department of Ophthalmology, University of Texas
22 Southwestern Medical School.

23 DR. VAN METER: Woodford Van Meter, private
24 practice of cornea and external disease in Lexington,

1 Kentucky.

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

5 DR. RUIZ: Richard Ruiz, professor and
6 chairman, Department of Ophthalmology at the University of
7 Texas, Houston.

8 DR. SONI: Sarita Soni, professor of optometry
9 and visual sciences at Indiana University School of
10 Optometry.

11 DR. McCLELLAND: Eleanor McClelland, University
12 of Iowa College of Nursing, associate dean and associate
13 professor there.

14 DR. GORDON: Judy Gordon, vice president of
15 research and development and regulatory affairs for Chiron
16 Vision, and industry representative to this panel.

17 DR. ROSENTHAL: Ralph Rosenthal, division
18 director, Division of Ophthalmic Devices, FDA.

19 DR. McCULLEY: At this point, I'd like to open
20 the public hearing portion of the meeting. Are there any
21 scheduled speakers?

22 MS. THORNTON: No, there are no scheduled
23 speakers, sir.

24 I'd like to read, for the record and for those

1 who may wish to speak, that speakers who will be making
2 presentations before the committee, if you so choose, are
3 doing so in response to the panel meeting announcement in
4 the Federal Register. They're not invited to speak by the
5 FDA nor are their comments, data, or products endorsed by
6 the agency.

7 If you wish to speak, you will be given
8 approximately a 10-minute limit. After speaking, the Chair
9 may ask you to remain if the committee wishes to question
10 you further. Only the Chair and members of the panel may
11 question speakers during the open hearing portion.

12 Dr. McCulley will recognize unscheduled
13 speakers at this time.

14 DR. McCULLEY: Is there anyone present who
15 wishes to speak?

16 (No response.)

17 DR. McCULLEY: Seeing no responses, that closes
18 the open public hearing period, and I would like now to
19 turn the meeting back to Ms. Thornton for further remarks.

20 MS. THORNTON: At this point in time, we'd like
21 to open the committee discussion period of the meeting, and
22 I will read into the record these remarks.

23 "The following announcement addresses conflict
24 of interest issues associated with this meeting and is made

1 part of the record to preclude even the appearance of an
2 impropriety. To determine if any conflict existed, the
3 agency reviewed the submitted agenda and all financial
4 interests reported by the panel participants. The conflict
5 of interest statute prohibits special government employees
6 from participating in matters that could affect their or
7 their employer's financial interest. However, the agency
8 has determined that participation of certain members and
9 consultants, the need for whose services outweighs the
10 potential conflict of interest involved, is in the best
11 interest of the government.

12 "A waiver has been granted for Dr. Woodford Van
13 Meter for his interest in an excimer laser firm that could
14 potentially be affected by the panel's deliberations. The
15 waiver permits this individual to participate in all
16 matters before the panel. Copies of this waiver may be
17 obtained from the agency's Freedom of Information Office,
18 Room 12A-15 of the Parklawn Building.

19 "For purposes of today's meeting, Dr. Doyle
20 Stulting, our Chairperson, is excluded from participation
21 due to the extent of his interest. Dr. James McCulley has
22 consented to serve in his absence.

23 "We would like to note for the record that the
24 ~~agency took into consideration other matters regarding Dr.~~

1 James McCulley. The financial interests reported by this
2 individual are not related to the matters before the panel.
3 Therefore, the agency has determined that he may
4 participant fully in the panel's deliberations.

5 "In the event that the discussions involve any
6 other products or firms not already on the agenda for which
7 the FDA participant has a financial interest, the
8 participant should excuse themselves from such involvement,
9 and their exclusion will be noted for the record.

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

15 "Pursuant to the authority granted under the
16 Medical Devices Advisory Committee Charter, dated October
17 27th, 1990, as amended April 20th, 1995, I appoint the
18 following individuals as voting members of the Ophthalmic
19 Devices Panel for the duration of this meeting on July
20 11th, 1997: Drs. Joel Sugar and Woodford Van Meter. For
21 the record, these persons are special government employees
22 and are consultants to this panel or consultants or voting
23 members of another panel under the Medical Devices Advisory
24 Committee. They have undergone the customary conflict of

1 interest review and have reviewed the material to be
2 considered at this meeting.

3 Signed, "Dr. D. Bruce Burlington, M.D.,
4 director, Center for Devices and Radiological Health,"
5 dated 6/13/1997.

6 Dr. McCulley?

7 DR. McCULLEY: At this juncture, we'd like to
8 ask Dr. Morris Waxler, the acting chief, Diagnostic and
9 Surgical Devices Branch, to introduce PMA P970001.

10 DR. WAXLER: It is a great pleasure to address
11 this panel. You have been selected by the agency because
12 of your scientific and clinical expertise in ophthalmology,
13 optometry, and vision science. We want you to focus your
14 attention on the clinical data which will be presented to
15 you today on the clinical trial conducted by the Emory
16 Vision Correction Center to determine the safety and
17 effectiveness of their LASIK device. We want your expert
18 advice about whether the data to be presented to you
19 demonstrated reasonable assurance of the safety and
20 effectiveness of this device.

21 FDA has defined the Emory medical device as
22 having four components: a nomogram, nomogram 2, for LASIK
23 ablation; two software packages developed by Summit
24 Technology, one single zone and the other multizone; the

1 approved Summit Technology Omnimed laser hardware; and an
2 automated microkeratome. Although discussion of the
3 ramifications of this definition at this meeting might be
4 interesting, we urge the panel to treat this medical device
5 as if it were one piece of equipment.

6 The agency has determined that the indication
7 for this Emory LASIK device will be as follows. The Emory
8 device is indicated for the LASIK treatment of myopia of
9 -1.0 diopter to -15.0 diopters with less than 1.0 diopter
10 of astigmatism. It is therefore important that the panel
11 discuss whether the applicant has provided sufficient valid
12 scientific evidence of the myopic range indicated.
13 However, there is no need to discuss whether the astigmatic
14 correction should be part of the indication.

15 The agency has decided that two claims of the
16 applicant will not be in the indication statement for this
17 device, but may be stated in the labeling. These two
18 claims are monocular monovision treatment and simultaneous
19 binocular surgery. We want the panel's expert advice about
20 how and if the information on these two claims should be
21 portrayed in the labeling.

22 As this is the first LASIK device to come
23 before the panel, we would appreciate having
24 ~~recommendations which will help set the benchmarks for~~

1 future applications.

2 I'd like to introduce the team leader for this
3 PMA, Daryl Kaufman.

4 DR. KAUFMAN: Good morning. I'm Daryl Kaufman,
5 the team leader for the Emory Vision Correction Center
6 LASIK PMA. I'd like to take a moment just to provide a
7 brief regulatory history of this application.

8 The Emory Vision Correction Center IDE G950058
9 was submitted on April 6th, 1995, and conditionally
10 approved on May 10th, 1995. Final approval was received on
11 July 21st, 1995. This initial submission formed the basis
12 for the Group 1 cohorts, since they were using the original
13 nomogram, nomogram 1, at that time. On August 29th, 1996,
14 FDA approved a clinical trial using the revised nomogram,
15 nomogram 2, for LASIK ablation. The PMA application
16 P970001 was filed with the FDA on January 17th, 1997, and a
17 filing letter acknowledging that the application was
18 sufficiently complete to permit a review was sent to the
19 sponsor on March 5th, 1997.

20 The primary panel reviewers for this
21 application are Dr. Woodford Van Meter, Dr. Marian S.
22 Macsai, and Dr. Joel Sugar. Panel input is required in
23 this area because clinical judgement is required to
24 evaluate this data. Your comments from the discussion

1 today will help us in assessing the safety and efficacy of
2 the device for the intended indication for use.

3 The review team evaluating the PMA and related
4 supplements included the following reviewers. A
5 statistical review was completed by Pamela Scott, with
6 consults from Dr. Judy Chin. Patient information labeling
7 was reviewed by Ms. Carol Clayton, and the clinical review
8 was completed by Dr. Malvina Eydelman. I would like to
9 thank these team members for the excellent job they did in
10 reviewing this PMA application, and in summarizing their
11 assessments so succinctly and expeditiously.

12 The sponsor will make their presentation of the
13 PMA at this time, followed by Dr. Eydelman's discussion of
14 her review.

15 DR. McCULLEY: I'd like to invite the sponsors
16 to the table and to begin your presentation, and to remind
17 you that you have up to one hour to present your data.
18 Also, please, as you begin your presentations, identify
19 yourselves.

20 DR. WARING: Good morning. I'm George Waring
21 from Emory University. We're pleased to present our PMA
22 this morning on the Emory LASIK System.

23 I acknowledge the individuals that are
24 assisting us this morning in presentation. I'll make an

1 initial presentation from our database, followed by Keith
2 Thompson, who will present the comparative data requested
3 by the agency. Dr. Jonathan Carr, our associate at Emory,
4 will provide some backup information for us. Ms. Wendy
5 Wiley, who is the project coordinator at Emory, will be
6 providing information for us, and Ms. Maureen O'Connell,
7 representing Summit Technology, will support us from the
8 technical side as well.

9 You might be asking yourself why a private
10 physician-sponsored IDE on LASIK was submitted and carried
11 all the way through to the PMA process. The answer to that
12 question derives from the initial presentations of the
13 excimer laser, with its Summit approval and VISX approval
14 that are quite familiar to you. While all that was
15 occurring, however, internationally LASIK was becoming a
16 very important procedure, and one that was felt to be
17 important by our colleagues internationally. LASIK was
18 felt by these individuals to be better than PRK because it
19 treated a wider range of myopia, had faster visual
20 recovery, less pain after surgery, it was easier to do an
21 enhancement, and it had become the procedure of choice
22 internationally, or was becoming that, at the time that the
23 PRK approvals were coming down in the United States.

24 ~~With this idea in mind, I went to Saudi Arabia~~

1 to study LASIK and to work out some of the details of that.
2 We did a number of trials over there, one published in the
3 AJO, another comparing LASIK in one eye versus PRK in the
4 other eye of the same patients, and my personal conclusion
5 was that LASIK was a preferable procedure to PRK.

6 However, there was little published data at
7 that time. Our paper was one of the first ones. We didn't
8 know very much about the formal safety and efficacy, and
9 indeed, at the time of PRK approval in the U.S., LASIK was
10 not a labeled indication for the use of the excimer laser.

11 So we decided that if we wanted to do LASIK at
12 Emory, and understand better what the procedure was, that
13 we would have to carry out our own Investigational Device
14 Exemption. Daryl Kaufman has indicated for you the history
15 of that in terms of our filing, and in terms of our filing
16 the PMA submission. After that filing, the agency worked
17 actively with us, which we appreciate very much, and we
18 filed five amendments to the PMA to clarify information,
19 and I'll present that as we go.

20 So the reason that we are here this morning
21 presenting to you as a physician-sponsored IDE is two
22 simple reasons. One, we would like to know more about the
23 safety and efficacy of the procedure ourselves and present
24 that information publicly, and two, we wanted to do LASIK

1 at Emory because we felt that this was in the best
2 interests of our patients. Yet, under the current
3 situation in the United States, we could not do so on
4 label. We would have to go off label. So for the last two
5 years, we have gone through the regulatory process, and
6 we're now seeking approval of our PMA so that we can do
7 LASIK at Emory.

8 The background objectives that we had were to
9 correct myopia from 2.0 to 30.0 diopters. You'll notice in
10 our labeling request we're asking only up to 15, and we'll
11 explain the reason for that as we go.

12 We had new laser software provided by Summit.
13 That software is not available in any other laser in the
14 United States, and we derived our clinical nomogram, which
15 converted the laser software that was written for PRK into
16 software that could be used for LASIK, by initially doing a
17 set of pilot cases, then studying a first group of eyes,
18 and then a second group of eyes. In other words, we've had
19 three different nomograms, and we are asking for approval
20 for our Group 2 nomogram. In addition, we've evolved
21 surgical techniques that I will outline for you.

22 The study design is simple. We studied
23 consecutive eyes. There are no exclusions. Fourteen
24 surgeons participated in this trial at Emory. Now, this is

1 very important because you are seeing data that's presented
2 as a real world, multiuser -- even though it's one site --
3 experience. This is not data coming from three skilled
4 surgeons who've had a lot of experience, but many of these
5 surgeons had their first experience as part of this trial,
6 so you are seeing real world data.

7 The database was frozen a year ago, and we have
8 filed amendments to our PMA during that time to keep it as
9 up to date as possible, and we'll present that to you, and
10 the panel has received copies of those amendments, but
11 please keep in mind that the original frozen database is a
12 year old.

13 We had five follow-up visits. We will be
14 emphasizing that the database is frozen and, at the time it
15 was frozen, we included all of the data from all of the
16 extant visits, from an eye exam at 24 hours after surgery
17 to an eye exam at 12 months after surgery. That is, we're
18 not presenting just a cross-section of data here that would
19 exclude a lot of eyes, but we're presenting to you every
20 eye that came through the study.

21 Some of you may not be familiar with LASIK, and
22 let us show you just a brief video clip of how LASIK is
23 done. As Dr. Waxler emphasized, the microkeratome and the
24 ~~whole procedure is part of our application. The procedure~~

1 is done outpatient, topical anesthesia only, lid speculum
2 after a prep and drape, and marking of fiduciary lines on
3 the cornea to line up the flap again when it's created.
4 The flap is 160 microns thick, made by the Chiron corneal
5 shaper, the automated corneal shaper, and this instrument
6 is different than the one that was used in ALK. It's
7 custom-made for LASIK.

8 The suction is raised to 100 above 65
9 millimeters of mercury, and you see that we check that with
10 the applanation tonometer, and the pressure really is about
11 90 millimeters of mercury, which occludes a central retina
12 while we are working. We moisten the surface so the
13 microkeratome will slide easily over the cornea. The
14 microkeratome is passed to the surgeon, placed into the
15 dovetails, the foot pedal is depressed, and the gears
16 propel the microkeratome forward and backward, and it's
17 stopped automatically by a stopper to create a hinge of the
18 flap. So we're not making a free disk. This is a hinged
19 flap.

20 The flap is then lifted up manually, folded
21 back on to the surface of the cornea, and only the
22 epithelial surface of the flap and epithelial surface of
23 the cornea contact each other. The bed, then, is revealed,
24 and the laser ablation is done on the bed in the exact same

1 fashion that you would ablate the surface for PRK, except
2 this is a surface in the stromal bed, and of course that
3 requires different algorithms in the laser and different
4 nomograms.

5 The flap is immediately put back into position
6 to decrease the chance of debris falling in the eye. There
7 is irrigation beneath the flap, which floats it up into
8 position, and then we smooth the flap out and it adheres
9 over the next two minutes by surface tension forces in the
10 endothelial pump.

11 Off the video, please.

12 We conducted this trial in two steps, in a
13 sense. That is, every patient received a primary procedure
14 and, as I'll discuss in a moment, we undercorrected on
15 purpose to prevent overcorrections, and went back and did
16 enhancement procedures as an integral part of our approach.

17 The clinical workups were a complete ophthalmic
18 examination that included brightness acuity testing and
19 contrast sensitivity testing, and all the data was entered
20 into the database. We did use the formal ETDRS NEI vision
21 charts throughout.

22 As Daryl mentioned, we have two groups of
23 patients. Group 1 is what we will present primarily this
24 morning. This is our largest group with the longest

1 follow-up, where we had a primary LASIK plus enhancements.
2 That was followed by the revised nomogram, which is Group
3 2, and this is the basis for our PMA request this morning,
4 and it consisted of the same type of surgery with just a
5 revised nomogram.

6 Within the trial, we had a number of subgroups,
7 and already Dr. Waxler has mentioned these to you. We
8 include all of the eyes in this report. We include the
9 pilot eyes, eyes that had previous surgery, eyes that were
10 done sequentially, eyes that were done simultaneously, and
11 so we're not making any exclusions, but we do not present
12 in our overall presentation the individual results of these
13 subgroups.

14 The Summit laser did not have facility to
15 correct astigmatism, and we corrected astigmatism with
16 arcuate transverse keratotomy in one out of five eyes.

17 The baseline refraction indicates that half of
18 the eyes were more than 7.0 diopters myopic, up to 22.0
19 diopters, so that half the eyes, if treated in the United
20 States today, could not have been treated by the excimer
21 laser with PRK. This is very important because it
22 emphasizes the expanded range that LASIK can treat.

23 Half the eyes had more than 1.0 diopter of
24 astigmatism. Now, whether to treat that astigmatism in our

1 trial was left to the surgeon's discretion. We did not
2 have an absolute cutoff, but we did use arcuate transverse
3 keratotomy, but that is not part of our PMA because that's
4 a matter of medical practice.

5 The accountability and follow-up was quite
6 good, around 90 percent up to three months, but then there
7 was a falloff at six and 12 months in our follow-up down to
8 about 70 percent. Why did we have poor follow-up at six
9 months? The reasons were simple. As you will see later,
10 the patient satisfaction was quite high, so patients were
11 not motivated to come back. In fact, the patients objected
12 to being dilated for cycloplegic exams. The exams were
13 thorough, they took over an hour, and patients objected to
14 coming back, particularly since they paid for this trial.
15 This was not done for free or at a discount, but at market
16 price.

17 Our resources at Emory were limited. We paid
18 for the trial out of clinical income. We had no extra
19 money for the trial, and we could not hire more personnel
20 to do the follow-up and to bring the patients in for
21 follow-up, so that's why we have a 70 percent follow-up at
22 six months.

23 Now, against that background then, let us
24 present to you our findings. We'll present two categories

1 of information, safety data -- and the safety data are
2 based on the intent-to-treat paradigm. That is, every
3 patient who entered the operating room, no matter what
4 happened to them, whether they were treated with the laser
5 or not, is entered into the safety data. There are no
6 exclusions.

7 The efficacy data, however, are based only on
8 patients who actually received the laser ablation, so we
9 can present to you how effective the laser ablation itself
10 was.

11 Let's start first, then, with the efficacy
12 information. This slide presents to you an overall feel
13 and look at how effective this LASIK procedure was. Here
14 is the mean refractive outcome presented over the 12-month
15 period. There were 208 eyes followed at every exam over
16 this 12 months, and it gives you a feel for the standard
17 deviation, for the stability of the procedure, and for the
18 overall efficacy. We'll talk about stability in detail in
19 just a minute.

20 The scattergram gives you a little better feel
21 at the last visit. That is, this is the last examination
22 on every patient, whether it was at two weeks or one year,
23 1,048 eyes representing our total database. From the
24 scattergram, with the red lines recommending 1.0 diopter

1 over or above the ideal outcome of 0, you can see that the
2 refractive change versus the preoperative refraction,
3 looking at a plano result, shows a general tendency toward
4 undercorrection.

5 This is our Group 1 data now, and this is done
6 on purpose, because we can do an enhancement procedure to
7 bring these eyes up toward emmetropia, but if an eye is
8 overcorrected, there is no good way, using current
9 technology, to bring the overcorrected eyes back down
10 toward emmetropia. So these eyes hanging below are there
11 on purpose, in a sense.

12 The overall refractive outcomes are presented
13 here. You can see that within plus or minus 1.0 diopter we
14 had about 85 percent of the eyes, and almost all of the
15 eyes falling within plus or minus 2.0 diopters, looking at
16 the eyes at the six-month interval in the blue bars and at
17 the most recent visit, whenever it was, in the yellow bars.
18 So 85 percent on the average here. A little bit better at
19 the last visit is the plus or minus 1.0 figure.

20 You'll notice again a trend toward
21 undercorrection here. More eyes are undercorrected than
22 overcorrected. We think this is very important for the
23 safety aspects on the refractive side. Overcorrected
24 patients are unhappy. Half of our patients are over age

1 40, so that we make an effort to undercorrect, and when we
2 present the Group 2 nomogram, the major revision in that
3 Group 2 nomogram has to do with shifting further toward
4 undercorrection to try to eliminate as much as possible
5 these overcorrected eyes.

6 The spectacle corrected visual acuity at
7 baseline is very important. I presented to you the
8 refractive results. Now, here are the visual acuity
9 results, but you'll see that a substantial number of eyes,
10 around 15 percent, could not see 20/20 or better at
11 baseline. Why not? Because the baseline refraction went
12 up to 22.0 diopters, and many of these higher myopes have
13 myopic choroal retinal degeneration that will not allow
14 them to see better. However, only a few eyes could see
15 worse than 20/40, so our 20/40 cutoff here is a very good
16 level to look at visual acuity outcomes.

17 The uncorrected visual acuity is presented to
18 you as the distance correction at six months or more
19 follow-up. We saw no point in presenting the earlier
20 visual acuities when the eye may still be settling, for
21 example, at two weeks. So these data are presented at six
22 months.

23 Please note that in these visual acuity data,
24 and here we have the visual acuity on the X axis and the

1 cumulative percent of eyes on the Y, that we have omitted
2 the eyes, 44 of them, where we specifically wanted to
3 undercorrect the eye for monovision. That is, to leave
4 -1.5 to 2.0 diopters for near vision. However, we did
5 include all of the other eyes here. We did not exclude any
6 eyes, even those that could not see 20/20 or better at
7 baseline.

8 You will see that 97.3 percent of these eyes
9 saw 20/40 or better at this follow-up. These are all eyes
10 within Group 1. Ninety-seven percent, 20/40 or better
11 without correction. That means only 2.7 percent of the
12 eyes saw worse than 20/40 without correction. We think
13 this shows in a very strong way the effectiveness of the
14 Summit laser and of the nomogram and algorithms that we
15 use.

16 One of the most important things that got us
17 interested in LASIK was the rapid visual recovery. Our
18 colleagues in South America and Europe were extolling the
19 virtues of LASIK because people could see well quickly, so
20 we looked carefully at this. We saw our patients at 24
21 hours after surgery, refracted them, took their visual
22 acuity, and you will notice that in Georgia, where the
23 cutoff is 20/60 for a driver's license, that 77 percent of
24 patients on the first morning after surgery could see 20/60

1 or better. That is, they had driver's level vision in
2 Georgia on the first morning, and indeed, a discouraging
3 number of them drove back to their first morning
4 examination because they could see quite well. This, of
5 course, is in contrast to PRK, as Keith Thompson will
6 present in just a moment.

7 Now, let's look in more detail at the stability
8 data. We've looked at refractive outcome. We've looked at
9 visual acuity. What about stability? You can see that on
10 the average stability is quite good. The change between
11 two weeks and three months, three months and six months,
12 six months and 12 months is less than 0.1 diopter. Let me
13 emphasize that. On the average, the change is less than a
14 tenth of a diopter at each interval after two weeks out to
15 one year.

16 Please note that these data are gathered on 208
17 eyes that were examined at every one of these four
18 intervals, and eyes that had no enhancement procedures. In
19 other words, we're presenting stability data on eyes with
20 only one LASIK procedure that were seen at every visit over
21 the one year. There are, in round numbers, 200 of those
22 eyes.

23 Now, we all know that there can be movement in
24 ~~the hyperopic and myopic direction that would make the~~

1 average look good, and here are those data. Between two
2 weeks and three months, between three months and six
3 months, and between six months and 12 months you can see
4 that approximately 10 percent of these eyes changed by 1.0
5 diopter or more. Here's the 1.0 diopter or more figure.
6 So that, although the average is very stable for 90 percent
7 of the eyes, approximately 10 percent of the eyes are
8 moving by 1.0 diopter.

9 But the interesting thing is that the number of
10 eyes moving in the myopic direction -- that is, gaining
11 minus power -- is approximately equal to the number of eyes
12 moving in the hyperopic direction -- that is, gaining plus
13 power. When we see this -- no particular trend toward
14 myopia, as you see after PRK, and no particular trend
15 toward hyperopic, as you see after RK -- we think that some
16 of this variability may be due to examination circumstances
17 and maybe some biological variability, but not a trend. We
18 still continue to think that after two weeks the refractive
19 outcome for LASIK is stable.

20 Those, then, represent the efficacy data:
21 refraction, visual acuity, stability. Let's look now at
22 the safety concerns. We divided safety into two aspects.
23 The first is the loss of two or more lines of the best
24 spectacle corrected visual acuity, always comparing to the

1 original baseline vision. That is, not the vision before
2 an enhancement, but we always compared to the vision taken
3 at baseline at entry. The second safety variable is
4 adverse events and complications.

5 Let's look first then at the loss of two lines
6 or more. Now, to provide full disclosure on safety to the
7 panel, we presented within all of the documents that you
8 have this rather complex method of presenting safety data,
9 but we thought it was fair that you have all of the data at
10 each visit. Each of these complex tables that you have for
11 each of the amendments and the original submission
12 indicates the number of eyes and the number of lines --
13 lost two lines, lost three lines, lost four lines -- at
14 each of the postoperative intervals after three months. We
15 did not concern ourselves with 24 hours and two weeks,
16 because we thought that was the instability of normal
17 healing. So those of you that want all the details, you
18 can look at every interval for every level of loss and see
19 how many eyes lost vision at those intervals.

20 We also looked at the loss at the last visit
21 after the primary surgery, before any enhancements, and at
22 the last visit or examination after the last surgery. Here
23 in this column, we are looking at information that includes
24 ~~24 hours and two weeks. In other words, the last time that~~

1 eye was examined. So we take that, we look at the total
2 number of eyes that lost two or more lines, deal with the
3 number of total eyes examined in that interval, and compute
4 the percentage of eyes losing two or more lines.

5 These are what I would call the raw data, and
6 we do realize that for the panel this is a little difficult
7 to digest. I mean, there's a lot of information with a lot
8 of data, but everything is disclosed.

9 To try to make sense out of that, what we did
10 was to take every eye that lost two or more lines, go back
11 as part of the amendment process, and examine that eye by
12 reviewing the chart. We looked at the chart at the last
13 examination, what we call the final visual acuity loss
14 report, and looked to see where is that eye right before
15 our panel discussion. This, then, takes care of patients
16 that might have lost, for example, two or more lines at
17 three months, but by 12 months had returned to their
18 baseline visual acuity. We think that this is the only
19 reasonable basis, the only reasonable figure, to judge in
20 looking at safety.

21 Now, here's an example. Here's our Group 1
22 data, all 1,048 eyes, and here are the number evaluated at
23 each of the follow-up visits, 1,063 in the final acuity,
24 and you will see that there is 8 percent losing two or more

1 lines at three months, but as we go out the follow-up curve
2 we look at the final visual acuity for each eye at its last
3 visit, and that's 4 percent of the eyes losing two or more
4 lines. We think this final acuity is the most important
5 document to see. We do have this type of an analysis for
6 each of the subgroups that the agency asked us to look at,
7 but I will not present them here. I'm only presenting the
8 Group 1 data, 4 percent losing two lines or more at the
9 final examination.

10 This is the overall pattern of change in visual
11 acuity, not just loss, but change in spectacle corrected
12 acuity. You can see that indeed there are more eyes that
13 gained spectacle corrected visual acuity than lost
14 spectacle corrected visual acuity. I'm sorry for this
15 small yellow print. That's way Harvard Graphics prints it,
16 but if you just look at the bars, the numbers are on the
17 top of the bars and you can see that at each point -- one
18 line, two lines -- that there are more gainers than losers.
19 So on balance, the patients are seeing better with their
20 spectacles after surgery than before.

21 Now, this table is extremely important, and let
22 me just go back and be sure that it's there. Thank you.
23 Rick understands this problem.

24 ~~This is the most important table that I can~~

1 present to you on safety, because we went back and looked
2 again at every chart on every eye that lost two or more
3 lines, and all of those patients, all of those eyes, are
4 represented in this table. You see the preoperative
5 spectacle corrected acuity, the postoperative at the last
6 visit, and the number of eyes that lost two, three, four,
7 or five lines. We have highlighted in white the three eyes
8 that lost to worse than 20/40 spectacle corrected acuity.
9 That is the level of cutoff in the guidance document.

10 So three out of the 1,063 examined at these
11 times, or .3 percent, lost two or more lines with spectacle
12 corrected acuity of 20/40 when compared to baseline.
13 Overall, the total number of eyes, as I mentioned already,
14 was 4 percent. That is, 43 out of the 1,063, or a 4
15 percent total loss, but .3 percent losing to worse than
16 20/40.

17 Now, what happened to these three eyes that
18 lost to worse than 20/40? The first patient was a patient
19 with penetrating keratoplasty previously. He was the first
20 eye -- he happened to be my patient -- the first eye that
21 we did LASIK over a PK. He had had keratoconus before and
22 we got a buttonhole in the flap because his cornea was
23 steeply curved, and we just didn't realize that at the
24 time. He did get some scarring in the area of the

1 buttonhole, and that gave him a loss of three lines of
2 spectacle corrected visual acuity.

3 The second patient had had a previous retinal
4 detachment repair, but had a visual acuity of 20/30
5 preoperatively. We also got a buttonhole in that case and
6 the flap was put back. The healing was rather good, but
7 during the postoperative period he developed an epiretinal
8 membrane. He was being followed on the retina service as
9 well, and his vision fell to 20/50, so it was probably
10 attributed not only to his maculopathy, but possibly to the
11 irregular astigmatism from the buttonhole flap.

12 The third patient was a physician with a
13 refraction of approximately -22.0 diopters who had a
14 technically successful LASIK, but had glare after surgery
15 and was placed on pilocarpine, pilocarpine in both eyes to
16 reduce his night glare, and he developed a retinal
17 detachment in the right eye that was not repairable, and
18 his visual acuity was approximately 20/100 at the last
19 visit.

20 Now, these represent the 0.3 percent of our
21 population that lost acuity down to less than 20/40. You
22 will notice that none of these eyes -- I'll emphasize again
23 -- none of these eyes were regular LASIK eyes. That is, a
24 simple myope that had a simple LASIK procedure. All had

1 some other circumstance, including the penetrating
2 keratoplasty, to complicate the situation.

3 Now, that was safety presented from the point
4 of view of losing two or more lines of acuity. Let's look
5 now at safety from the point of view of adverse events and
6 complications. Please remember that our study commenced
7 before the agency issued its guidance document on excimer
8 laser surgery, so we did not have benefit of formal
9 definitions of adverse events and complications.

10 Therefore, in our initial document, we defined an adverse
11 event as an unexpected event that threatened visual acuity,
12 and we defined a nonadverse complication as an unexpected
13 event that did not directly threaten visual acuity.

14 For example, a buttonhole flap is an adverse
15 event, because it creates an irregular flap and irregular
16 astigmatism that threatens acuity, but a free flap, cut all
17 the way through with the loss of the hinge that can be
18 replaced normally during surgery, does not constitute an
19 adverse event because the surface remains unaffected and
20 smooth, but it does constitute a complication.

21 Now, in the documents that you have we have
22 reported every adverse event, we have followed every eye
23 out to its last examination, and we have documented for you
24 ~~the findings at every examination for every adverse event.~~

1 All those details are in the documents in our PMA.

2 For purposes of this presentation, we will put
3 together adverse events and complications, and when we
4 combine those, you will see first of all that all but one
5 of these complications is a flap complication. Five
6 percent of the eyes had a complication in this series, and
7 here we're talking about 1,281 operations. That is, the
8 primary operation plus the enhancement operations.

9 Now, we did have our one retinal detachment
10 that I explained to you. We do not think that that's due
11 directly to LASIK, but in a population of 1,000 eyes, one
12 retinal detachment, particularly to -22.0 diopters, I think
13 is to be expected.

14 Please note that half the flap complications
15 were during surgery and half were after surgery. Now, what
16 are the details of this? Well, let's look at the
17 complications during surgery. We had small flaps, large
18 flaps, incomplete flaps, thin flaps, thick flaps, split
19 flaps, and you see the number here.

20 The important number in this slide is right
21 here. Of the 27 intraoperative complications, only two of
22 the eyes lost two or more lines of spectacle corrected
23 visual acuity, and both of those had a buttonhole in the
24 flap. The other flap complications, we were able to

1 reposition the flap in a way so that we reapproximated
2 baseline visual acuity. One of these eyes went to 20/25
3 and was not ablated. The other eye went to 20/60 and was
4 not ablated. So these are these two.

5 I'm sorry. This is incorrect. This should be
6 ablated. This is a typographical error, because one of
7 these was ablated, one was not, and this loss to 20/60
8 represents the guy with the maculopathy that I described to
9 you with a previous retinal detachment, who had a laser
10 with ablation -- that's this one eye that was ablated --
11 but then got the maculopathy postoperatively and the vision
12 fell.

13 The postoperative flap complications include
14 mostly slippage, epithelial ingrowth, two eyes of the same
15 patient that had inflammation, and two eyes that had large
16 folds. Again, only one of these 40 eyes with this type of
17 postoperative complication had a loss of spectacle
18 corrected acuity of more than two lines, but none of them
19 to a loss of more than 20/40, so the postoperative
20 complications we could manage.

21 Now, the largest number here is epithelial
22 ingrowth, and please notice that in the guidance document
23 that came out after we commenced this trial epithelial
24 ingrowth is considered an adverse event. We don't think

1 this is completely accurate. Let me explain why.

2 Epithelial ingrowth comes in a wide variety of
3 severity. At every visit, we formally graded epithelial
4 ingrowth as between trace, 0.5, up to 4.0+ severity, so we
5 have formal prospective data on epithelial ingrowth.
6 You'll see that of the eyes that had epithelial ingrowth,
7 the vast majority had Grade 0.5 to Grade 1.0. That is the
8 7 percent here.

9 What does this mean? This means that there are
10 a few cells at the edge of the flap that are not
11 progressive. Often, these cells just atrophy and leave a
12 little gray spot, so we do not consider these to be adverse
13 events.

14 However, eyes with Grade 2.0 or more, 23 of the
15 eyes or 1.8 percent of this population, we do consider to
16 be a complication or adverse event, and we had to go back
17 in on 1.8 percent of these eyes and clean out the
18 epithelium. We can present more detail on that later if
19 the panel is interested.

20 Now, in terms of overall safety, where do we
21 stand? That is, in terms of these complications with the
22 flap. Here are the data for the 19 surgeons operating at
23 Emory from the first quarter of our trial out to the
24 seventh quarter of our trial. You can see the number of

1 complications and the percentage of complications during
2 this particular clinical trial over a year and a half time.
3 You'll notice a steady decrease in these complications. In
4 other words, there is a learning curve to LASIK, but the
5 curve can be learned, and we combined the sixth, seventh,
6 and eighth quarters because we had a smaller number of eyes
7 and the complication rate intraoperatively was less than 1
8 percent.

9 Now, to what do we attribute this increasing
10 safety of the procedure over time? Well, first of all, why
11 did we have the complications? There were problems with
12 the microkeratome and the blade, there were problems with
13 the patients, who may be poorly cooperative or not have
14 enough room around the eye, and there were problems with
15 the surgeon not knowing how to handle the instruments well.
16 All three of these -- instrument, patient, and surgeon --
17 are problems that can be managed, as we have shown by the
18 increasing safety of the procedure over the 18 months of
19 this trial.

20 What did we do to increase our safety? We
21 trained the surgeons. We had a formal credentialing
22 program. We videotaped every case and reviewed the cases
23 that had difficulty, and this led to the fact that three of
24 the 14 surgeons I mentioned 19 a minute ago, and that

1 was wrong -- either dropped out or were asked to drop out
2 of the trial because they were not comfortable doing LASIK.
3 So we had strict enforcement criteria for our
4 credentialing, and the increasing safety is quite apparent
5 during this trial in terms of the complications and adverse
6 events.

7 I presented, then, in safety loss of two or
8 more lines, adverse events and complications, and let's
9 look at the question of the endothelium. Some people raise
10 the question, if you make a 160-micron flap and you ablate
11 closer to the endothelium, could the shockwave or other
12 factors damage the endothelium with LASIK, whereas you
13 wouldn't damage the endothelium with PRK?

14 We carried out a prospective trial examining
15 eyes with central noncontact specular microscopy pre-op,
16 two weeks post-op, and 12 weeks post-op, according to
17 baseline refractive error. In other words, these eyes with
18 higher corrections had the treatment closer to the
19 endothelium than these eyes with lower corrections. You
20 can see that there is no difference in endothelial cell
21 count during these three intervals post-op, there's no
22 difference based on baseline refraction, and this is true
23 of hexagonality, and this is true of coefficient of
24 variation of cell size. This paper will come out in the

1 AJO shortly.

2 Another safety factor we looked at is contrast
3 sensitivity. This is our Group 1 data, the contrast at the
4 last examination after the most recent surgery, so it
5 includes enhancements. We examined contrast at four
6 spatial frequencies, 3, 6, 9, and this should be 18 cycles
7 per degree, and we noticed a very interesting thing. First
8 of all, there were increases and decreases in contrast
9 sensitivity using the sine-wave vector vision charts, and
10 at the lower spatial frequencies we noticed more loss of
11 contrast than gain, but at the higher spatial frequencies
12 we noticed more gain than loss.

13 Now, maybe this is just a simple magnification
14 factor. That is, we get rid of the minification of the
15 baseline myopic spectacles, and therefore the patients can
16 see the required higher resolution of the higher
17 frequencies. We're not sure of this, and to be quite
18 honest we're not completely sure how to interpret all of
19 these data.

20 I want to conclude this presentation now in
21 response to the agency's request that we present also Group
22 2 data and that we present data on eyes that had LASIK
23 only, no ARC-T. These slides will summarize that, first of
24 all with the data we've already presented. Here's your

1 baseline data, Group 1, all eyes, 1,048 cases, and then
2 here is Group 1 LASIK only, Group 2 with the new nomogram
3 that we're asking for approval for, all eyes, 800, and
4 Group 2 LASIK only.

5 So you can see that within plus or minus a half
6 a diopter the numbers are almost the same, 50 percent, and
7 that plus or minus 1.0 diopter the numbers are very
8 similar, 75 to 80 percent, so there's comparability to the
9 large data I presented to you in these other groups, LASIK-
10 only Group 2.

11 In terms of overcorrections, the new nomogram
12 did work. That is, the Group 2 eyes had half as many
13 overcorrections, about 1 percent, compared to the Group 1
14 eyes, where there was actually about 3 percent
15 overcorrection. So this is why we think the Group 2
16 nomogram is preferable for treating these patients, and
17 please notice that the LASIK-only eyes had very similar
18 findings to the eyes that had LASIK plus ARC-T in both
19 groups.

20 In terms of safety, you can see that in losing
21 two or more lines, at the last surgery the results are
22 worse in the Group 2 data, and this is simply because many
23 of these eyes are followed only at three months and have
24 not had time to stabilize. There's a lot of two week data

1 in here.

2 If, however, you look at the last available
3 acuity, which is, remember, the examination of each eye,
4 you can see that the safety is quite good in each of the
5 other groups. We had 4 percent loss, as I presented
6 before, of two or more lines, but that went down to 1.8
7 percent LASIK only in Group 1, 1.1 percent in Group 2 all
8 eyes, and 1.2 percent Group 2 LASIK only. So the safety
9 level with the loss of acuity is very good across the board
10 and a little bit better than our core data that I have
11 presented to you.

12 My final slide addresses the patient. At 12
13 months, we administered a formal questionnaire to our
14 patients. This is the exit questionnaire, if you please,
15 and we had about 140 people at the time the database was
16 frozen that completed this questionnaire. We asked a lot
17 of questions, but there are two very important questions
18 here that I'll present the results of to you.

19 One of the questions was how often do you wear
20 glasses and what percent of patients wear glasses none or
21 part-time? In other words, were we successful in the
22 patient's goal of getting out of corrective lenses? The
23 answer is yes, we were. Ninety-two percent of the eyes --
24 ~~or the patients, not eyes. These are patients, not eyes.~~

1 Ninety-two percent of the patients were able to go either
2 never or part-time -- for example, night driving -- without
3 glasses. We think this shows efficacy at the patient
4 level. In terms of satisfaction, 90 percent of the
5 patients said they were satisfied or highly satisfied with
6 the outcome of the surgery at 12 months.

7 So this represents the summary of our outcomes
8 data. Dr. Thompson will now present data based on
9 comparative findings.

10 DR. THOMPSON: Thank you, George.

11 I'm Keith Thompson, an associate professor of
12 ophthalmology at Emory, and one of the co-investigators in
13 this study.

14 DR. McCULLEY: Excuse me. I just want to
15 remind the presenters you have another 20 minutes for your
16 presentations.

17 DR. THOMPSON: We'll be complete. Thank you,
18 Dr. McCulley.

19 The agency requested that we provide
20 information comparing data from our study and data
21 presented for alternative treatments, and particularly
22 that's data familiar to this panel and the agency regarding
23 low to moderate myopia under 7.0 diopters. For this, we
24 have a wealth of information available at present in the

1 Summit and VISX PMA applications. I'll also tell you how
2 our data compares with the benchmarks established by the
3 recent FDA guidance document.

4 Now, a direct comparison of the Summit and VISX
5 PRK data and our results is not appropriate. It would be
6 an apples to oranges comparison. In fact, our patients
7 were much more myopic than those in the PRK studies, they
8 had more astigmatism, many, as Dr. Waring indicated, had
9 best spectacle corrected visual acuity less than 20/20, and
10 many of our patients had an intentional undercorrection for
11 purposes of monovision. Therefore, in order to provide the
12 panel a reasonable comparison, we have selected a subset of
13 our data of our patients treated under 7.0 diopters of
14 myopia and with astigmatism less than 1.0 diopter. We also
15 excluded those patients who intentionally requested an
16 undercorrection for monovision.

17 Let's then try make an apples to apples
18 comparison of how the results from LASIK with the Emory
19 system compare to PRK as performed with the VISX and Summit
20 systems. In terms of safety parameters, we'll look at the
21 data at six months loss of two lines or more of best
22 spectacle corrected visual acuity.

23 All of the format of the slides here will be
24 the same. Summit data will be on the left, VISX next, the

1 Emory subset data then, and where a benchmark is available
2 from the FDA guidance document, it will be presented last.

3 At six months, we see that 6.8 percent of the
4 Summit 6 millimeter patients had lost two lines, 5.1
5 percent for VISX, and only 2.8 percent for the Emory
6 subset. This number is well below the benchmark
7 established by the agency in its guidance document.

8 Looking at loss of two lines and vision worse
9 than 20/40 best spectacle corrected at six months,
10 fortunately very few eyes altogether, none for Summit, 0.6
11 percent for VISX, 0.4 percent for Emory, and again, all
12 below the FDA guidance document benchmark of 1 percent.

13 Corneal clarity is another important safety
14 parameter. There's a lot of concern about haze following
15 PRK in those studies. We also, in our slit lamp exam,
16 rated the clarity of corneas in a similar fashion. This
17 data is available from our subset compared to that data
18 available for the Summit PRK study. Similar data was not
19 presented in the VISX PRK summary.

20 You will notice that LASIK does not cause
21 hazing or clouding of the central cornea, that by and large
22 there's excellent corneal clarity preserved with LASIK, and
23 this is no surprise to us physiologically, because Bowman's
24 ~~layer in the epithelium is left intact centrally and~~

1 subepithelial wound healing is not induced.

2 Let's compare the efficacy of LASIK versus PRK
3 under 7.0 diopters. Unaided vision, 20/40 or better at 12
4 months, excellent for Summit at 98.8, 95.1 for VISX, a
5 similar value for our subset, and all of these are higher
6 than the FDA's benchmark of 85 percent.

7 For 20/20 or better at 12 months, 80 percent
8 for Summit, 63.7 for VISX, and 56 for our subset. We were
9 somewhat surprised by this initial result and we sought to
10 explain it, and looked backed at the data. I'd like to
11 point out to members of the panel that if we look at the
12 percentage of patients that were overcorrected by more than
13 1.0 diopter at six months, we find that over 5 percent of
14 patients undergoing PRK with Summit or VISX were
15 overcorrected. Very few of our patients in this subset
16 were. Note also that the mean age of the patients in the
17 PRK studies was younger than our cohort with a mean age of
18 42.

19 DR. BULLIMORE: Can I ask you to go back one
20 slide just temporarily? Is that 12 months or six months?

21 DR. THOMPSON: This is 12-month data or last
22 visit for our subset.

23 Predictability, refractive outcome within 1.0
24 diopter, here we see 85.3 percent for Summit, 90 percent

1 for VISX, 91 percent for our subset under 7, excellent
2 predictability for LASIK under 7.0 diopters. Within plus
3 or minus a half, again the data shown for you here, 69.2
4 percent for our subset, comparing favorably with PRK and
5 exceeding the benchmark established by the FDA's guidance
6 document.

7 Here's an important slide. This compares the
8 stability of refractive outcome at two-week or one-month
9 intervals, three month, six month, and 12 month. This data
10 is, again, available for the Summit PRK data and compared
11 with our subset. This indicates whether the population at
12 this interval has achieved refractive stability. There are
13 still statistically significant changes underway in
14 patients that have undergone PRK at one month, whereas in
15 this subset, as well as in the larger data set that Dr.
16 Waring shared with you, patients achieve stability at two
17 weeks following LASIK.

18 Recovery of vision is an important efficacy
19 parameter. Now, this 24-hour data was not available and
20 not measured for the PRK PMA summaries. However, we
21 treated 75 eyes in Phase III at our institution, so data
22 was available on these patients. None of these patients
23 achieved 20/40 or better vision on the first postoperative
24 visit at 24 hours, but in our subset under 7.0 diopters, 70

1 percent were already seeing 20/40 or better postoperative
2 day 1, so LASIK affords patients a very rapid recovery of
3 vision.

4 What about pain following surgery? Again, a
5 very important differentiating feature. This data was
6 available in the VISX summary. Thirty percent of patients
7 reported moderate to severe pain following PRK. We
8 performed a recent phone survey of 50 consecutive patients
9 with a similar grading scale. Only one patient in 50
10 reported moderate pain, and the rest, 98 percent, reported
11 either none or mild pain.

12 Now, the panel may make a criticism of this
13 comparison, because data that I'm presenting to you, some
14 of these patients have undergone enhancements. I'd like to
15 point out that everything I've shared with you so far is
16 LASIK-LASIK information. In other words, the primary
17 procedure was LASIK only with no arcuate keratotomy, and
18 the enhancement procedure was LASIK only as well. Fourteen
19 percent of these patients underwent an enhancement, none in
20 the Summit data set, and only 3.6 percent underwent a
21 retreatment with VISX.

22 I would argue for you, though, that the ease of
23 enhancements allows a surgeon using LASIK to refine the
24 ~~initial outcome and avoid overcorrecting patients. For~~

1 example, if we look at the refractive scatter, refractive
2 predictability, we see that all refractive surgical
3 procedures have some inherent unpredictability, and LASIK
4 is no exception. The best parameter of predictability is
5 the standard deviation of the spherical equivalent at any
6 given interval, and if you look at the 12-month intervals,
7 you see that they're about the same for these three
8 studies, .66 for Summit, .78 for VISX, and .61 for our
9 subset.

10 Let's take a look at the refractive surgeon's
11 dilemma, then, if he is operating with a procedure with an
12 inherent unpredictability. Suppose you're presented with a
13 5.0 diopter myope who desires a goal of emmetropia. The
14 procedure's outcome has a standard deviation of 0.7, about
15 what we see in these studies. What target outcome should
16 the surgeon choose for this patient? Recall that 95
17 percent of patients will fall within two standard
18 deviations of this target outcome.

19 If the surgeon targets plano, on average 8
20 percent of his patients will be overcorrected by 1.0
21 diopters or more, and 24 percent will be overcorrected by a
22 half diopter or more. In fact, if you look at the Summit
23 data at one year for their 6 millimeter data, 9.8 percent
24 were overcorrected by 1.0 diopters or more at 12 months.

1 That closely approximates this prediction.

2 What the surgeon should do, then, if he wishes
3 to avoid overcorrections, which cannot today be treated, is
4 to target for an undercorrection, and if he chooses -0.65
5 as his outcome, he will only overcorrect less than 5
6 percent of his patients by a half diopter or more.

7 However, he will produce a 30 percent undercorrection rate.
8 That is, almost a third of his patients will then be
9 undercorrected by more than 1.0 diopters. These patients,
10 if they desired emmetropia, will probably be unhappy.

11 So the advantage that LASIK offers the surgeon
12 is that you can target undercorrection, allow the eye to
13 stabilize, and then perform -- you have the video,
14 Jonathan? -- an enhancement procedure to refine the
15 refractive outcome.

16 Enhancements were performed in our study.
17 We'll show a brief video here. Enhancements were performed
18 after the three-month postoperative visit to insure that
19 the refraction had become stable. The edge of the flap is
20 identified, and the edge raised with a Sinsky hook or
21 similar instrument, so the original bed is exposed, laser
22 treatment is applied, and then the flap is reflected back
23 in position.

24 ~~We think the ability to refine or modify the~~

1 outcome as soon as refractive stability is achieved is a
2 big advantage to this procedure.

3 You can have the video off, please, and the
4 slides back on.

5 This was what was performed in our study,
6 enhancements at three months. Now, the advantage, of
7 course, is you can reduce the number of overcorrections,
8 and if you compare this with the Summit data at 12 months,
9 you'll see that we achieve far fewer overcorrections, which
10 today cannot be treated.

11 So in summary, I've tried to give the panel and
12 the agency an apples to apples comparison under 7.0
13 diopters. We see that in terms of safety parameters LASIK
14 equals the PRK data in terms of preservation of visual
15 acuity and exceeds that in terms of corneal clarity.
16 Regarding efficacy, unaided visual acuity is similar,
17 predictability is similar, LASIK offers earlier stability,
18 a more rapid visual recovery, less pain, and the
19 flexibility to modify the outcome. In all cases, LASIK
20 performed with the Emory system exceeded the safety and
21 efficacy parameters established by the agency.

22 Let me move on quickly in the next three or
23 four minutes to discuss LASIK versus alternative treatments
24 available for patients who are over 7.0 diopters. Here we

1 look at automated lamellar keratoplasty, a study published
2 last year, as well as some unpublished data from our
3 institution, and also included in comparison is a recently
4 published study with PRK. The number of patients, the mean
5 refractive error range, and follow-up interval are
6 summarized for you in this table, and we can look at a few
7 safety and efficacy parameters among these groups.

8 Looking at loss of two lines or more of best
9 spectacle corrected acuity, Price's study with ALK lost 6
10 percent, 14 percent with the same surgeons presenting this
11 LASIK study with ALK, 8 percent with McCarty PRK under 10,
12 and notice that 22 percent -- 22 percent -- of patients in
13 McCarty's study over 10 lost two lines or more of best
14 spectacle acuity. Eight percent of our subset over 7.0
15 lost two lines.

16 Looking at efficacy, unaided vision 20/40 or
17 better, the Emory LASIK subset over 7.0 clearly outperforms
18 PRK in a similar range, and I'll point out that although 83
19 percent of our patients that had ALK several years ago at
20 Emory achieved 20/40 or better, these patients took an
21 average of 2.1 operations to achieve their outcome versus
22 about 1.25 operations in our LASIK subset.

23 Refractive predictability with 1.0 diopter,
24 here again showing an advantage for the Emory LASIK System

1 over 7.0.

2 So to summarize, we think that in terms of
3 safety and efficacy that LASIK with the Emory system
4 exceeds available alternatives. Therefore, on the basis of
5 the data that we've presented to you today, and I would
6 like to thank you for your attention, we request FDA
7 approval for the Emory LASIK System. We think that safety
8 has been demonstrated and that probable benefits to
9 improving patients' vision outweigh the probable risk. We
10 think we've demonstrated data that the effectiveness of the
11 Emory LASIK System provides clinically meaningful and
12 significant results for patients who wish to decrease their
13 dependence on corrective eyewear. We therefore request FDA
14 approval for the Apex and Apex Plus laser with Version
15 2.6.2 software and the Emory Group 2 nomogram treating
16 myopia from -1.0 to -15.0 diopters in this system.

17 Thank you very much for your attention.

18 DR. McCULLEY: Does that conclude the sponsor
19 presentation?

20 DR. THOMPSON: Yes.

21 DR. McCULLEY: We have one question for
22 clarification.

23 DR. MACSAI: Dr. Thompson, was this data where
24 you compared 1.0 to 7.0 with less than 1.0 diopter of

1 astigmatism new data?

2 DR. THOMPSON: No, it was not.

3 DR. MACSAI: In my review -- maybe the FDA can
4 clarify for me if that subset was subset out in Amendment 4
5 and 5.

6 Dr. Eydelman, did I receive it prior to this
7 meeting?

8 DR. EYDELMAN: Dr. Eydelman, FDA. You have not
9 received it and I have not received it. We have requested
10 of the sponsor that if any new analysis of the data that
11 was presented in the PMA is presented at this meeting, that
12 they specifically clarify which of those analyses are new,
13 so perhaps we can go back and do that exercise again.

14 DR. McCULLEY: Can we ask you for a quick
15 summary of what is new that you're presenting now for the
16 first time that no one in the review group has seen?

17 DR. EYDELMAN: Me or --

18 DR. McCULLEY: I think Dr. Thompson.

19 DR. THOMPSON: Well, first, to answer the
20 original question, all of the data that I presented under
21 7.0 is in the original submission.

22 DR. MACSAI: Right, but it's not separated out
23 with less than 1.0 diopter of astigmatism --

24 DR. THOMPSON: That's correct.

1 DR. MACSAI: -- as you've presented it today.

2 DR. THOMPSON: That analysis was performed
3 subsequently.

4 DR. MACSAI: This is new.

5 DR. THOMPSON: Yes, ma'am.

6 DR. MACSAI: So we've not had a chance to
7 review it. Is that correct?

8 DR. WARING: May I comment, please? George
9 Waring. We did this in response to a specific request --

10 DR. MACSAI: I know.

11 DR. WARING: -- from the FDA during the
12 amendment process, and as you can imagine, it's not easy to
13 go back and find the data, redo our analysis with a subset,
14 and we were not able to accomplish the response to the
15 agency's request in time to include it in an amendment.
16 That is, the amendments had all been mailed out already for
17 review, we asked the agency what to do, they said please
18 bring your information and present it, and we'll discuss it
19 there, even though it represents new information that did
20 not make it by the deadline of the amendment.

21 So let me be very clear, this is not an
22 analysis that was in our study protocol. It was an
23 analysis done in response to the agency's request very
24 recently.

1 DR. McCULLEY: Thank you. I think that
2 clarifies your position.

3 Would the FDA like to clarify the situation
4 further?

5 (No response.)

6 DR. McCULLEY: I think what we'll do at this
7 point is ask the sponsors to depart the table, we will take
8 a break, and then we will reconvene with the FDA clinical
9 review.

10 (Recess.)

11 DR. McCULLEY: I call the session back to
12 order. Dr. Rosenthal has a comment to make, please.

13 DR. ROSENTHAL: I just wanted to clarify the
14 issue of what material can be presented and cannot be
15 presented. It's agency policy that material that is
16 submitted to the agency and within the database of the
17 agency can be presented at this meeting. It is, however,
18 good politic to inform the panel and the agency at this
19 meeting that the material is new to us. It's within the
20 database, but it is presented to us in a different form
21 from which we or the panel had received it, and that's what
22 the controversy was with Dr. Thompson's presentation. It's
23 legitimate to present it, but the panel and the FDA have
24 ~~not received it, and I would suggest that at future~~

1 opportunities you present it saying it has not been
2 included in the packet.

3 Thank you very much.

4 DR. McCULLEY: A point of clarification as well
5 is that we were just now handed hard copy of what I presume
6 were both Drs. Waring's and Thompson's presentation. Is
7 that correct?

8 DR. WARING: Yes, sir.

9 DR. McCULLEY: We just received that now. We
10 did not receive it earlier.

11 The FDA review will be presented by Dr.
12 Eydelman.

13 DR. EYDELMAN: Thank you. Good morning.

14 Dr. Thompson has just eloquently demonstrated
15 that we should be careful not to compare apples and
16 oranges. Since this PMA has numerous variables and
17 parameters in it, I would start out by trying to define
18 what is the apple in this PMA.

19 The Emory Vision Correction Center is
20 requesting FDA's approval of the medical device which is
21 comprised of the following: an automated microkeratome;
22 Summit Technology Omnimed laser hardware; Summit Technology
23 laser software, single zone, which is currently approved in
24 the United States for PRK for eyes with myopia less than or

1 equal to 7.0 diopters at the spectacle plane, and multizone
2 software, Version 2.6.2, not previously approved for
3 marketing in the U.S., for eyes with high refraction; and
4 revised nomogram for LASIK ablation.

5 The clinical protocol for this study was
6 originally approved for treatment of myopia up to 30.0
7 diopters. In the investigation, myopia was treated for
8 spherical equivalent refraction from -0.25 to 21.25
9 diopters. The data analysis revealed that although LASIK
10 is technically capable of correcting myopia up to 22.0
11 diopters, the corrections greater than 15.0 diopters were
12 more likely to have subtle wrinkles in the flap, a less
13 accurate refractive outcome, and glare symptoms under
14 dilated pupil conditions. Therefore, the proposed
15 indication is up to 15.0 diopters.

16 Astigmatism from 1.0 to 4.0 diopters was
17 treated in this trial using arcuate transverse keratotomy.
18 The sponsor considers the ARC-T operation a matter of
19 medical practice, and is not requesting this as an
20 indication in this PMA.

21 According to the LASIK nomogram, single zone
22 treatment is used for laser settings of 7.0 diopters or
23 less. At this setting, 310 pulses are delivered to the
24 central cornea. Assuming a nominal ablation rate of .25

1 microns per pulse, this should remove 78 microns of tissue.
2 Adding this to the thickness of the flap, which is no more
3 than 160 microns, the last pulse should fall at the depth
4 of 238 microns from the original level of the epithelium.

5 For multizone ablations, the sponsor has
6 provided an example in this PMA of the calculations for
7 18.0 diopters of ablation. Since the upper limit requested
8 in this indication is 15.0 diopters, this number was of
9 greater interest to us. I have recently reviewed the
10 prophilometry data available to us for the Summit multizone
11 software with the FDA engineers. We have concluded that
12 for the maximum correction requested of 15.0 diopters, 285
13 microns of tissue will be removed from the original level
14 of the epithelium.

15 A nomogram of the desired correction, based on
16 the preoperative refraction, was created as part of the
17 original IDE. The subjects treated with this nomogram
18 comprise Group 1. Review of the initial results of the
19 combined computer algorithm clinical nomogram revealed that
20 some eyes were overcorrected. Therefore, a revised
21 nomogram 2 was derived to minimize overcorrections without
22 necessitating an inordinately large number of enhancements.
23 This nomogram was used on a new cohort of subjects,
24 referred to as Group 2. The sponsor intends to use only

1 nomogram 2 after approval is obtained.

2 Combined LASIK and arcuate transverse
3 keratotomy were used as a primary procedure in subjects
4 with 1.0 diopter or more of astigmatism. The results of
5 astigmatism treatment are presented in this PMA for
6 completeness and to demonstrate the overall efficacy of the
7 combined LASIK and ARC-T techniques. However, the sponsor
8 is not asking for labeling or approval of astigmatic
9 correction. I will therefore limit my remarks today to a
10 group of patients treated with LASIK only during the
11 primary procedure.

12 Group 1 recruitment lasted from May 10, 1995,
13 to August 30, 1996. Data collection and analysis of these
14 subjects is continuing. Group 2 recruitment began
15 September, 1996, and is still continuing. The fact that a
16 lot of subjects treated have not yet reached many of the
17 follow-up visits is reflected in this graph of the number
18 of eyes examined at each visit as of the time of the last
19 amendment submission.

20 Out of 840 eyes treated in Group 1, 733 were
21 examined at three months, 423 at six months, and 205 at 12
22 months. Even though 205 eyes are less than a quarter of
23 the eyes treated, it constitutes 55.3 percent of the eyes
24 eligible for the 12 month examination as of today. For

1 Group 2 eyes, 352 out of 705 treated were examined at three
2 months, and only 22 eyes so far have been examined at six
3 months.

4 When one analyzes the accountability of just
5 the subjects that reached the appropriate exam, the numbers
6 also decrease rapidly with time. There were no deaths
7 during this trial. The sponsor informed us that they're
8 trying to contact all eligible subjects who were not
9 examined at a particular visit. The sponsor's definition
10 of loss to follow-up was not clear from the original
11 submission. In a recent telephone conversation, the
12 sponsor clarified that the subject is not considered by
13 them lost to follow-up until after the 12-months follow-up
14 visit time.

15 This definition of loss to follow-up differs
16 from the usual FDA definition. According to FDA's
17 definition, for example, for Group 2 at six months, loss to
18 follow-up would be 41 percent.

19 This table demonstrates several important
20 points about preoperative refraction which need to be
21 considered when evaluating the appropriate dioptic range
22 for this indication. The original sponsor's proposed
23 indication had a lower limit of 2.0 diopters, and the
24 ~~revised indication had a lower limit of 1.0 diopter. There~~

1 were five eyes in Group 1 and 21 eyes in Group 2 with a
2 manifest refraction between -1.0 and -1.99 diopters.
3 Fifteen diopters is the current higher limit for the
4 indication. Between 14.0 diopters and 14.99 diopters,
5 there were a total of four eyes treated in Group 1 and six
6 eyes in Group 2.

7 Even though the sponsor's upper limit of the
8 proposed indication is 15.0 diopters, the sponsor states
9 that the procedure can be done up to 20.0 diopters at the
10 surgeon's discretion in individual cases of severe
11 intolerance of spectacle and contact lens correction. In
12 this study, there were 24 eyes treated, combining Groups 1
13 and 2, with refractions between 15.0 and 21.99 diopters.

14 In most of the discussion in the PMA, the
15 sponsor quotes results after the last surgery. In this
16 table, however, I have plotted the results after the
17 primary procedure for eyes undergoing LASIK only. At three
18 months after the primary procedure, 22 percent of eyes in
19 Group 1 were 20/20 or better. The number increased to 36
20 percent at six months and 48 at 12 months. For Group 2, 28
21 percent were 20/20 or better at three months. As I
22 mentioned previously, there is a very small number of eyes,
23 22 in Group 2, which were followed out to six months, thus
24 ~~making any conclusions about outcomes questionable at that~~

1 time point. Vision of 20/40 or better was reached by 68
2 percent of Group 1 at three months, 83 at six months, and
3 87 at 12 months.

4 In this figure, I have summarized the sponsor's
5 report of UCVA results by baseline refractions. I have
6 combined the lower myopic ranges into one group with
7 baseline refractions from -0.15 to 6.99 in order to compare
8 results to target safety and efficacy endpoints delineated
9 in FDA's guidance on refractive lasers for myopia below 7.0
10 diopters.

11 For myopes below 7.0 diopters, UCVA of 20/40
12 was achieved after primary LASIK by 70.8 percent Group 1
13 eyes at three months and 84 percent at six months. For
14 Group 2, 79 percent of eyes at three months and 61 percent
15 at six months achieved 20/40 or better. As mentioned
16 previously, the six-month Group 2 results are probably
17 artificially low due to the limited follow-up.

18 The guidance recommends for myopes under 7.0
19 diopters that a minimum of 85 percent of eyes should reach
20 UCVA of 20/40 or better at a point of stability for the
21 device. The 83.8 percent of Group 1 at six months is
22 certainly close to 85 percent. However, since the sponsor
23 in the formal submission did not separate out the eyes
24 ~~treated for monovision, no meaningful comparison can be~~

1 carried out for the data as currently supplied.

2 After the primary procedure, 38 percent of
3 Group 1 and 41.6 percent of Group 2 were within plus or
4 minus 0.5 diopters of emmetropia. The numbers increase at
5 six months for Group 1 to 52 percent. Sixty-four percent
6 of Group 1 and 67 percent of Group 2 eyes were within plus
7 or minus 1.0 diopter of emmetropia at three months,
8 increasing to 78 percent at six months for Group 1.

9 The sponsor does not provide attempted versus
10 achieved analysis, and does not separate out the eyes
11 intentionally undercorrected. The information is also not
12 broken down by the preoperative refractive error. Thus, it
13 is impossible to make any valid comparison to the guidance,
14 which recommends a minimum of 75 percent of eyes with
15 myopia under 7.0 diopters to have an achieved refraction
16 within plus or minus 1.0 diopter of the attempted
17 refraction, and at least 50 percent of the subjects to be
18 within plus or minus 0.5 diopters of the attempted.

19 The current refractive guidance recommends as a
20 safety target that less than 5 percent of subjects lose
21 more than two lines of best spectacle corrected visual
22 acuity. It is interesting to point out that at two weeks
23 7.7 percent of Group 1 eyes had loss of greater than two
24 lines of best spectacle corrected. The sponsor was asked

1 to address this apparent discrepancy concerning a claim in
2 the original PMA submission of refractive stability after
3 two weeks and spectacle corrected visual acuity returning
4 to baseline in the vast majority of eyes at three months.
5 The sponsor suggested that the overall refractive state of
6 the cornea stabilizes early, but the quality of vision and
7 the visual acuity takes longer to return to baseline
8 because of subtle postoperative changes in the cornea.

9 Enhancements under the protocol could be
10 performed with LASIK only, arcuate transverse keratotomy
11 only, or a combination of LASIK and ARC-T. In Group 1, 370
12 eyes, which was 44 percent, underwent any enhancement
13 procedure, and in Group 2 115 eyes, which was 16 percent,
14 had an enhancement so far. In Group 1, 5 percent had two
15 enhancements and .8 percent had three enhancements.

16 Because of the definition of the device in
17 question, I felt it was important to concentrate on the
18 outcomes of patients who received only LASIK for the
19 primary procedure and only LASIK for all enhancements. In
20 Group 1, 140 or 21 percent of the eyes had a LASIK-only
21 enhancement. In Group 2, 81 or 21 percent had a LASIK-only
22 enhancement.

23 Here, I have summarized the post-enhancement
24 refractive results presented by the sponsor in Amendment 5.

1 Of the eyes in Group 1 that received one enhancement with
2 LASIK only, 77 percent had a refraction within plus or
3 minus 0.5 diopters. In Group 2, 40 out of 46 eyes, which
4 is 87 percent, at two weeks after one LASIK-only
5 enhancement had a refraction within plus or minus 0.5
6 diopters. Eighty-eight percent of Group 1 had a refraction
7 within plus or minus 1.0 diopter at three months, and 100
8 percent of Group 2 were within plus or minus 1.0 diopter at
9 two weeks.

10 Very limited follow-up is available as of today
11 on Group 2 post-enhancement results at greater than two
12 weeks. Data on more than one enhancement procedure with
13 LASIK only is also very limited and therefore inconclusive.

14 It is interesting to compare the outcomes of
15 the primary procedure versus those after the first
16 enhancement. One can readily see from this graph why post-
17 enhancement results are the ones that are most often
18 quoted.

19 In contrast to photorefractive keratectomy,
20 most published data demonstrates that LASIK provides
21 stability for practical clinical purposes after month 3.
22 In the original PMA submission, the sponsor analyzed the
23 means of the refractive outcomes and also concluded that
24 ~~the data demonstrate excellent overall stability early in~~

1 the postoperative period. Therefore, submission and panel
2 presentation of this PMA based upon the current follow-up
3 data was felt to be appropriate.

4 FDA's statistical analysis, however, concluded
5 that although the presented table of manifest refraction at
6 each visit is an indicator of when stability may have
7 occurred, it treats the refraction at a visit as a discrete
8 parameter independent of the refraction from another visit.
9 In order to demonstrate stability, we requested a table
10 that treats refraction as a continuous unit that could vary
11 over time; i.e., a difference table of the refraction
12 between consecutive exams for individual patients. The
13 sponsor was asked to provide this data for subjects who
14 have had every follow-up exam up to the 12 months in order
15 to validate the stability claims.

16 This analysis has been carried out and
17 submitted to the agency. I have plotted this data in this
18 graph. These are the 95 percent confidence intervals of
19 the mean difference in refraction at various time
20 intervals. This means, basically, that for 95 percent of
21 the eyes the refractive change between three months and two
22 weeks will be within +2.7 to -2.61 diopters. The
23 refractive change between three and six months will be
24 within +1.42 to -1.47, and between 12 months and six months

1 will be within +1.38 and -1.27.

2 Current refractive guidance defines refractive
3 stability as a change of less than or equal to 1.0 diopter
4 of manifest spherical equivalent refraction between two
5 refractions performed at least three months apart. The
6 panel is being asked to discuss the interpretation of
7 stability data for this device, and whether the sponsor
8 needs to provide further analysis of stability data.

9 One of the outcomes studied in this trial was
10 the effect of simultaneous versus sequential surgery.
11 Sponsor presents a three-month analysis of 215 eyes treated
12 sequentially and 270 eyes treated simultaneously. Vision
13 of 20/40 or better was achieved by 66.7 and 66.9 percent of
14 sequential and simultaneous subgroups, respectively. 42.6
15 of sequentially treated eyes were within plus or minus 0.5
16 diopters, as compared to 34.7 percent of simultaneously
17 treated eyes.

18 With regards to safety, 4.7 and 4.8 percent of
19 eyes in sequential and simultaneous subgroups had a loss of
20 two or more lines of best spectacle corrected visual
21 acuity. Adverse events occurred with a rate of 0.9 percent
22 among sequentially treated eyes and 1.1 percent of
23 simultaneously treated eyes. If we do some statistics, we
24 can say that for a sample size of 200 and an observed

1 adverse event rate of 1 percent, it is likely that the true
2 rate is between 0.12 and 3.57 percent, with a two-sided 95
3 percent confidence limit.

4 I would also like to point out an adverse event
5 that occurred in one patient operated bilaterally in this
6 study. The patient developed diffuse hazing infiltrates
7 throughout the entire interface of both eyes. All
8 microbiological studies were negative and the inflammation
9 cleared with a good refractive result at three months. The
10 impression was an idiopathic keratopathy, possibly caused
11 by toxic materials, such as blade cleaning compounds, that
12 got in the bed during surgery.

13 The sponsor is asking for labeling for
14 monocular surgery. Monocular surgery was studied in this
15 trial in subjects with anisometropia due to previous
16 surgery leaving residual myopia in one eye, subjects
17 wishing surgery in one eye only to retain monovision in the
18 unoperated eye for near work, and some subjects who could
19 simply not afford surgery in both eyes. Separate analysis
20 of safety and effectiveness outcomes for these eyes have
21 not been provided.

22 Keeping those highlights of the study in mind,
23 we would like you to address the following questions. This
24 PMA presents data on 1,545 eyes which underwent only LASIK

1 as a primary procedure. Eight-hundred forty of these eyes
2 were treated with the original nomogram and 705 eyes with
3 the revised nomogram. Follow-up data at 12 months is
4 submitted for 205 eyes treated with the original nomograms.
5 Follow-up data on eyes treated with the revised nomogram is
6 available for 352 eyes at three months and 22 eyes at six
7 months. The applicant is requesting PMA approval of the
8 nomogram only. The sponsor has not submitted a refractive
9 stability analysis for the eyes treated with the revised
10 nomogram.

11 Analysis of refractive stability for the eyes
12 treated with the original nomogram demonstrates that for 95
13 percent of the eyes, the refractive change between three
14 and six months is within plus or minus 1.5 diopters and
15 between six months and 12 months within plus or minus 1.3
16 diopters. Current refractive guidance for myopia less than
17 7.0 diopters defines refractive stability as a change of
18 less than or equal to 1.0 diopter of manifest spherical
19 equivalent refraction between two refractions for 95
20 percent of the eyes treated.

21 A. Has adequate refractive stability been
22 demonstrated with the original nomogram at six months? At
23 12 months?

24 B. FDA has recently recommended that the

1 sponsor analyze separately stability data for eyes with
2 refractive error below 7.0 diopters of myopia for ease of
3 comparison to our refractive guidance. Does the panel feel
4 that a breakdown of stability data into subsets of 0 to 7.0
5 and above 7.0 allows them to better evaluate the outcomes
6 of this device?

7 C. Is the current definition of refractive
8 stability in the guidance appropriate for studies with
9 higher myopic error?

10 D. Based on the refractive stability presented
11 in this PMA, is the current follow-up of eyes treated with
12 revised nomogram sufficient to provide reasonable assurance
13 of safety and effectiveness of this device?

14 Question number 2. For ease of comparison to
15 our refractive guidance, FDA has recently recommended that
16 the sponsor analyze separately all safety and efficacy
17 endpoints for eyes with refractive error below 7.0 diopters
18 of myopia. The agency has not received or reviewed this
19 stratified analysis. FDA review is based only upon the
20 safety and effectiveness outcomes for the full range of
21 myopia from -1.0 to -15.0 diopters.

22 A. Is a stratified analysis of these data
23 critical to a recommendation of reasonable assurance of
24 ~~safety and effectiveness of the applicant's device?~~

1 B. What, if any, additional data analyses are
2 needed to make the decision?

3 Question number 3. Do the testing results on
4 contrast sensitivity, glare, and topography provide
5 reasonable assurance of safety and effectiveness of this
6 device?

7 Question number 4. Which of the following two
8 options does the panel feel is the appropriate endpoint for
9 the comparison to safety and effectiveness targets outlined
10 in our refractive guidance? Is it safety and effectiveness
11 results after the primary refractive correction only or
12 outcomes after all enhancements? And is your
13 recommendation appropriate for all future LASIK devices?

14 Question number 5. The sponsor has requested
15 approval of their device for simultaneous LASIK surgery.
16 How does the panel feel the data regarding simultaneous
17 surgery should be presented in the labeling?

18 Question number 6. The sponsor has requested
19 approval for monocular surgery. In this PMA, monocular
20 surgery was defined as surgery on one eye of a patient
21 which was performed for one of the following reasons:
22 anisometropia secondary to previous surgery leaving
23 residual myopia in one eye; patient wanting a surgery in
24 one eye only to retain monovision in the unoperated eye for

1 near work; and patient capable of affording surgery in one
2 eye only. How does the panel feel the data regarding
3 monocular surgery should be presented in the labeling?

4 Question number 7. A subjective patient
5 satisfaction questionnaire was administered to all patients
6 in this study at the 12-month visit. However, no
7 psychometric data were submitted to FDA. The sponsor is
8 planning to submit the results of the questionnaire after
9 all subjects complete the 12-month examination. Will the
10 results of the patient questionnaire influence the panel's
11 recommendations regarding approval of this device?

12 Thank you very much for your attention.

13 DR. McCULLEY: Does that conclude the FDA's
14 presentation?

15 DR. EYDELMAN: Yes.

16 DR. McCULLEY: At this point, I'd like to ask
17 if there are specific questions from the panel of the FDA
18 relative to the presentation we just heard.

19 DR. BULLIMORE: Dr. Eydelman, this is Dr.
20 Bullimore speaking. When you presented the enhancement
21 data, the percentages you presented, were they only for the
22 enhancement patients or the primary procedure plus
23 enhancement patients?

24 DR. EYDELMAN: It was only for those patients

1 who have received LASIK only as a primary, followed by
2 LASIK only as enhancement.

3 DR. BULLIMORE: So the denominator, if you
4 like, was only the patients who had two LASIK procedures.

5 DR. EYDELMAN: Correct.

6 DR. BULLIMORE: You didn't include the patients
7 that had only one.

8 DR. EYDELMAN: Correct.

9 DR. BULLIMORE: I guess the next question's
10 redundant, but I'll ask it anyway. The follow-up times
11 were relative to their second procedure, relative to the
12 enhancement?

13 DR. EYDELMAN: Yes.

14 DR. McCULLEY: They were relative to the
15 enhancement.

16 DR. EYDELMAN: To the enhancement, yes.

17 DR. HIGGINBOTHAM: This is Dr. Higginbotham.
18 Dr. Eydelman, I take it there was no quality of life data
19 either submitted to FDA.

20 DR. EYDELMAN: Can you repeat the question? I
21 didn't hear you.

22 DR. HIGGINBOTHAM: Any quality of life data?

23 DR. EYDELMAN: No, there was not.

24 DR. McCULLEY: Are there any other questions

1 for Dr. Eydelman? You're leaning toward the mike. Are you
2 thinking about it?

3 DR. MACSAI: I'm thinking about it.

4 DR. McCULLEY: Dr. Macsai.

5 DR. MACSAI: This is Dr. Macsai. Dr. Eydelman,
6 in past panels, it's come up that when there's not
7 conclusive evidence or data for the FDA, we've asked you
8 why you brought it to panel, and I can't help but ask that
9 question again, because you repeatedly stated there was
10 inconclusive evidence to come to a conclusion.

11 DR. ROSENTHAL: Would you like me to answer
12 that?

13 DR. EYDELMAN: Go ahead.

14 (Laughter.)

15 DR. McCULLEY: Dr. Rosenthal.

16 DR. ROSENTHAL: It was felt that the issue of
17 LASIK is one which is of paramount importance, both to the
18 clinical community and to the laser manufacturing
19 community, and I felt it was not unreasonable to bring this
20 to you for advice with regard to setting certain standards
21 that are going to be required for future panel discussions
22 or future submissions. Hence, though it was not perfect, I
23 made the decision, with Dr. Eydelman's concurrence, that we
24 would bring it to you.

1 DR. MACSAI: Dr. Macsai. Now, another
2 question, then, Dr. Rosenthal. Are we laying out standards
3 for a LASIK guidance document at this meeting in addition
4 to reviewing the Emory Vision Center's PMA?

5 DR. EYDELMAN: This is Dr. Eydelman again. We
6 only ask your guidance about other LASIK devices regarding
7 specific questions which I have outlined, nothing else.
8 There are two questions, I believe, where we felt we didn't
9 have enough guidance for our future reviews, and I have
10 tried to separate out the questions so it's clear where
11 we're talking about this PMA as opposed to all future LASIK
12 devices. If you need further clarification, I'll be happy
13 to do that.

14 DR. McCULLEY: You okay?

15 DR. MACSAI: I'm fine.

16 DR. ROSENTHAL: May I also add that if you feel
17 there are other aspects of the existing guidance document
18 which may not be relevant to the LASIK procedure or which
19 may change, we would like your advice on that in a general
20 discussion, but the specific issues are the ones which Dr.
21 Eydelman presented, and I think are the issues which this
22 PMA presented as difficulties and which may be more
23 difficult in future submissions, if I've made myself clear.

24 DR. McCULLEY: Are there any other questions

1 for the FDA before we go on to our panel reviewers?

2 (No response.)

3 DR. McCULLEY: Seeing none, thank you very
4 much.

5 Dr. Woodford Van Meter, Dr. Joel Sugar, and Dr.
6 Marian Macsai are the primary reviewers on this PMA, and
7 we're going to start off with Dr. Van Meter.

8 DR. VAN METER: Thank you. I appreciate the
9 large amount of data presented by the sponsors and
10 Malvina's wonderful review, which was helpful.

11 My review of the safety and efficacy of PMA
12 P970001 is based on the data submitted in the original PMA
13 and updated in five amendments. The safety data can be
14 culled from the populations treated by both nomograms,
15 Group 1 and Group 2, but the effectiveness data that we
16 should concentrate on is predominately weighted on the
17 Group 2 patients that were treated with LASIK only.

18 The speed of visual rehabilitation after LASIK
19 and the relative absence of postoperative pain show that
20 LASIK can be more satisfying to patients than PRK.

21 However, patients with lower myopia did better than
22 patients with higher myopia. According to the sponsor's
23 explanation, the higher myopes were more likely to have
24 residual myopia that was potentially treatable by repeat

1 LASIK, and in general the higher myopes were more likely to
2 have myopic retinal changes.

3 In a subgroup of patients that were separately
4 analyzed, they could see 20/20 or better with spectacle
5 correction before surgery. Approximately 50 percent of
6 these patients saw 20/20 or better uncorrected, 80 percent
7 20/25 or better, and 97 percent saw 20/40 or better
8 following the last procedure, so it clearly is effective.

9 However, to review the data, it would be nice
10 for us to have intended versus achieved data, which was not
11 provided, and I think it would be helpful to have data
12 stratified at least perhaps 7.0 diopters or less, and then
13 7.0 to 15.0 diopters, and longer follow-up, since this is
14 the patient population that we're interested in approving,
15 would also be helpful.

16 Overcorrection is the most serious problem that
17 we have with postoperative refractive error, and 8.4
18 percent of Group 1 patients were overcorrected by more than
19 half a diopter, and yet only 1.5 percent of Group 2
20 patients were overcorrected, using the overall patient
21 population as the denominator. Presumably, this is because
22 a lot of the Group 2 patients had not yet reached the stage
23 at which they would have their enhancement procedures, so I
24 think in favor of avoiding overcorrection the ability to

1 target an undercorrection and enhance probably makes sense,
2 because it's hard to deal with overcorrections.

3 The stability of the refraction data that was
4 calculated by Dr. Eydelman's review shows that a mean
5 change of less than 0.1 diopter exists for all intervals
6 examined. However, the standard deviation between three
7 and six months and six and 12 months is about 0.7 diopters,
8 with a 95 percent confidence range of plus or minus 1.45
9 diopters in the three- to six-month interval, and plus or
10 minus 2.5 diopters for 95 percent confidence in the six- to
11 12-month interval. So some data out past three months
12 would be helpful to ascertain that the results are indeed
13 stable.

14 Intraoperative complications occurred in 26
15 patients and were related, according to data presented, to
16 the surgeon in 76 percent, the patient's eye in 20 percent,
17 and the keratome in 4 percent. Careful thought would make
18 it hard to blame any of these on anyone but the surgeon,
19 and this shows the importance of learning curve in this
20 procedure. Interface debris, dust, metallic particles, and
21 epithelial cells were reported under the flap and seemed to
22 be related to learning the use of the keratome. All of
23 these complications were less frequent in Group 2 than in
24 Group 1.

1 The effect of surgical skill on the outcome of
2 this device is significant, and the wrinkles which were
3 noted in the flap, which are not known to affect visual
4 acuity, are probably also related to surgeon technique, and
5 this should be a very, very careful issue with labeling. I
6 think the sponsors appreciate the importance of surgeon's
7 skill and learning curve.

8 Let me speak briefly to complications. The
9 complications predominately arise from cutting the flap,
10 rather than administering the laser treatment. Cutting the
11 flap is a technically precise surgical procedure that
12 depends on mechanical reliability of the corneal shaper or
13 the skill of the surgeon, and it assumes a reasonably
14 normal corneal architecture in the patient. All of these
15 probably point to the surgeon as the predominant cause of
16 these intraoperative-related complications, so training of
17 the surgeon is important for use of the keratome, and the
18 ability to recognize those eyes which might have a less
19 than optimal result is also critical.

20 Let me suggest several points in conclusion. I
21 believe that six months is a suitable time frame for safety
22 and efficacy considerations to not expect additional
23 complications, but because of the wide range of 95 percent
24 confidence limits of 2.5 diopters from six to 12 months,

1 longer follow-up data I believe would be helpful.

2 I believe the safety and efficacy data support
3 conditional approval of the PMA, but the approval should be
4 based on discussion of the following considerations. It
5 would be nice to have additional data collection from the
6 Group 2 patients, following all of their enhancements,
7 because right now we think their endpoints are going to
8 look good, but we don't have that data.

9 Continued monitoring of contrast sensitivity
10 data to explain the variations in the loss of lower spatial
11 frequency and the gain of higher spatial frequency would be
12 helpful, and continued monitoring of corneal topography.
13 Until we can understand that, the variations reported in
14 the last handout that we got are meaningless, and our
15 suspicion is that they probably are within the acceptable
16 realm of corneal topography for refractive surgery.

17 I think there needs to be even an increased
18 emphasis from what we've discussed on surgeon training, and
19 there should be appropriate disclosure to the patients that
20 most of these complications occur in the early portion of
21 the surgeon's learning curve, and there is a potential
22 liability issue here that I don't think we can do anything
23 about.

24 ~~The loss of two or more lines of best spectacle~~

1 corrected visual acuity at two weeks and at three months is
2 high, but it's probably not unreasonable given the
3 experience with corneal refractive surgery, either RK or
4 lamellar grafts, and the fact that even following
5 penetrating keratoplasty or long-term contact lens wear
6 visual acuity is down, and the data out at six months and
7 beyond appears to be exceptional.

8 I would like to ask several questions of the
9 sponsor, which can be addressed either at the conclusion of
10 my review or another one, and that is can you tell me, in
11 your list of complications which were ranked by quarter,
12 the denominator of patients went down over the last five or
13 six quarters, and was this because fewer patients were
14 being entered into the study or fewer patients were being
15 operated on for LASIK?

16 My second question, what happened to the 10
17 percent of patients that were not satisfied at the one-year
18 survey? Did they receive additional treatment or do we
19 know why they were not satisfied with their procedure?

20 Could you address, just from experience or from
21 your data, are there any complications that occurred due to
22 enhancement procedures? We don't know whether the
23 interface haze, epithelial debris, and metallic whatever --
24 I presume they're related to the microkeratome. Is there

1 any reason to think that additional enhancement procedures
2 increase debris on the epithelial interface?

3 Finally, in the data that Dr. Thompson
4 presented, there was an 8 percent loss of two or more lines
5 of best spectacle corrected acuity in your subgroup of
6 patients over 7.0 diopters. This got washed out in the
7 overall data, but could you please address this higher than
8 expected loss of acuity?

9 DR. McCULLEY: Does that conclude your
10 questions?

11 DR. VAN METER: That concludes my review.

12 DR. McCULLEY: I think we'll hold all questions
13 until all three of the primary reviewers have presented.

14 Dr. Sugar?

15 DR. SUGAR: Thank you.

16 My response is a little less formal because
17 I've changed things as we've gotten more information. The
18 data has been very well laid out by Dr. Eydelman, who did a
19 spectacular job, I think, of reviewing an incredible amount
20 of data and making it easier for us to review.

21 The outcomes in Group 1 with 87 percent seeing
22 20/40 or better certainly meet the guidelines. In Group 2,
23 on the data that we have, which is still moving, 78 percent
24 saw 20/40 or better uncorrected, which does not yet meet

1 the guideline, but time is required.

2 It is very difficult, in reviewing the data,
3 although it's presented as last initial and last surgery,
4 last initial being the last visit before an enhancement and
5 the subsequent information being after enhancements,
6 certainly it's appropriate in my mind, looking at the data,
7 to look at it as a procedure with enhancements. That is, a
8 procedure that requires enhancements. Forty-four percent
9 of those in Group 1 with LASIK only required enhancements
10 and 16 percent in Group 2 thus far have undergone
11 enhancements, and I think it's important that the package
12 insert and in fact the labeling emphasize the fact that
13 this should not be presented to the patient as a single
14 procedure, but as a procedure with a high likelihood of the
15 need for enhancements.

16 In the area of safety, in Group 1, 2.2 percent
17 lost greater than two lines of best spectacle corrected
18 acuity at three months, and in Group 2, 0.8 percent lost
19 the same amount at three months, but the numbers were
20 small. Overall, as of the last visit, 0.6 percent were
21 worse than 20/40, with data accrued as of June 10th, and I
22 think that that's reasonable and certainly within the
23 guidelines.

24 ~~Adverse events were seen in 1.1 percent of~~

1 Group 1 and 0.9 percent of Group 2. One new patient was
2 added to Group 2 in the updated information. I think an
3 important patient was added that had a bacterial keratitis
4 within 24 hours. The patient was operated on on May 29th,
5 and I assume that there is more follow-up available, but
6 the patient had unilateral surgery and had unilateral
7 bacterial keratitis within 24 hours. To the best of my
8 knowledge, that's the only documented infection, but it's
9 important to emphasize that infection can occur because of
10 violation of the corneal stroma.

11 The stability data I think are as yet
12 insufficient in Group 2 for us to draw conclusions. The
13 brightness acuity testing showed that in Group 1, including
14 all patients, only 1 percent lost two or more lines and saw
15 less than 20/40 with the BAT on medium. In Group 1 LASIK
16 only, that was 1.2 percent and in Group 2, as of now, there
17 are no patients that fell into that group. That is, who
18 dropped below 20/40 with a BAT on medium.

19 Contrast sensitivity showed loss at low spatial
20 frequencies and gain at high spatial frequencies. This has
21 been discussed. The clinical significance of this is
22 certainly uncertain to me, and untested. We saw yesterday
23 some driving data and other ways of analyzing this
24 information in a practical sense, and I'm not asking that

1 the sponsors do this, but it would be nice to understand in
2 a practical sense what this data means, and I don't
3 understand it.

4 The topographic analyses which we were
5 presented on patients who had lost acuity show highly
6 variable topographies with some irregular patterns, but
7 they do not appear to directly correlate with acuity. I
8 don't think you can look -- these were ISIS analyses -- and
9 draw any conclusions. We did not, however, see analyses of
10 patients who didn't have problems, and I don't know if in
11 the aggregate that data looks different than the patients
12 who did have problems.

13 In summary, the procedure appears to be
14 effective and relatively safe. I'm uncertain about the
15 stability. I suspect that we have enough information to
16 conditionally approve this technique. Adequate training of
17 surgeons must be mandated because of the steep learning
18 curve. Informed consent must include information
19 concerning the high frequency of enhancements. The issues
20 of simultaneous versus sequential surgery and monocular
21 versus binocular surgery I don't think we should address,
22 because I think the issues remain practice of medicine
23 issues.

24 Thank you.

1 DR. McCULLEY: Dr. Macsai?

2 DR. MACSAI: Thank you, Dr. McCulley.

3 First of all, I think I'd like to congratulate
4 the sponsors, because I think this is a landmark study.
5 It's the first scientific prospective study of LASIK, which
6 is out being touted to the lay population without any good
7 data, and though the initial study was very complicated
8 with the multiarms that were attempted to be looked at,
9 Amendments 4 and 5 made it much easier to review.

10 I also want to compliment Malvina on making
11 that which I couldn't understand initially understandable.

12 Much of what I want to say has been addressed.
13 There are still some points, though, I think we need to
14 talk about. As we know, all these patients were treated at
15 the Emory Vision Correction Center in northern Atlanta, and
16 the majority of the patients enrolled in the study were
17 Caucasian. This may, in some way, skew the data. Though I
18 can't be sure, I think it needs to be pointed out.

19 Of the 14 patients who participated in the
20 initial study, my impression was that three surgeons
21 withdrew because they were uncomfortable with the surgical
22 procedure, not that they didn't do it well enough. Then
23 three other surgeons were added to the group, but this
24 demonstrates the degree of complexity of this surgical

1 technique.

2 As far as looking at safety and adverse events,
3 perhaps due to the haste in preparing the documents, some
4 of the numbers changed in different places, and it was very
5 difficult to figure out if in Group 1 the 21 eyes that had
6 problems were all due to the microkeratome, and in Group 2
7 were the eyes due to the microkeratome or the slit flaps or
8 epithelial ingrowth. For me, I need a little bit more
9 clarification of exactly those adverse events.

10 But regardless of the analysis, clearly, this
11 level of adverse events reflects the complexity of the use
12 of the microkeratome and inherent errors that may result
13 either as a result of the corneal shaper or the surgeon
14 that is using it. Stratification of the number of
15 complications per surgeon demonstrates no identifiable
16 trend, and the complications per number of procedures is
17 higher during the initial use of the microkeratome, and in
18 fact, in Group 1 five of the adverse events occurred during
19 the initial procedures being performed under supervision by
20 surgeons during certification.

21 But it's important to note the incidence of
22 adverse events did not decrease to zero with the eyes in
23 Group 2, demonstrating that despite a steep learning curve,
24 ~~there continues to be a low, but significant, incidence of~~

1 adverse events even in the hands of the most experienced
2 surgeons.

3 The sponsors outlined a detailed training and
4 certification program for surgeons using this new
5 technique. However, there clearly remains areas for
6 improvement in the technology of the corneal shaper and the
7 potential for a higher incidence of adverse events in the
8 hands of less experienced surgeons.

9 As far as stability, I'm not a statistician,
10 but if you look at Group 1, primary LASIK only, visual
11 acuity better than or equal to 20/40. In patients less
12 than 7.0 diopters, 70.8 percent achieved this vision at
13 three months, and this increases to 83.8 percent at six
14 months. The same trend is followed for every group you
15 look at. If you look at the number of patients in Group 1,
16 LASIK-only primary procedure, if you look at the group that
17 is plus or minus a half diopter, it's 38 percent, and that
18 increases to 51 percent at six months. Again, plus or
19 minus 1.0 diopter is 64 percent, and that increases to 75
20 percent at six months.

21 Then at the same time, the number of loss of
22 two lines of best spectacle corrected visual acuity starts
23 off at 2.2 percent at three months, and then it decreases
24 to 1.4 percent at six months. So all of this makes me

1 think that we should be looking at the data at six months.
2 The data's better. The patients see better. It must not
3 be stable at three months if all the percentages are going
4 up or down. That's my conclusion.

5 As far as endothelial cell damage, the studies
6 of Dr. Edelhauser concluded there were no clinically
7 significant changes that I think we need to worry about.

8 As far as epithelial ingrowth, Dr. Waring
9 showed that a high percentage of patients have epithelial
10 ingrowth of some type, whether it's Grade 0.5 to Grade 4.0,
11 and some of those patients need surgical intervention to
12 remove the epithelial ingrowth. Dr. Sugar just said that
13 one patient in Group 2 has developed bacterial keratitis.

14 MS. THORNTON: Excuse me, please. Would you
15 please refrain from taking pictures at this time?

16 I'm sorry, Marian.

17 DR. MACSAI: That's okay.

18 One patient developed bacterial keratitis. I'm
19 concerned that we haven't followed patients long enough as
20 far as epithelial ingrowth, because an intraocular surgery
21 epithelial ingrowth can proceed, and maybe some of this
22 epithelial ingrowth at the margin of these flaps will get
23 worse and require more intervention. We don't have enough
24 data on the epithelial ingrowth of the enhancements, and

1 since some patients took as many as two to three
2 enhancements, and that's going to be requiring another
3 opening of the flap, another opening of the stroma to the
4 atmosphere and potential infection, we have to monitor that
5 in some way over a longer period of time.

6 So you have to kind of look at the
7 enhancements, too, and as was said earlier, 44 percent of
8 patients in Group 1 needed enhancements and 16 percent in
9 Group 2. So the large number of enhancements demonstrates
10 the safety of the enhancement technique if the majority of
11 the adverse events were the result of microkeratome
12 failures. However, the amount of epithelial ingrowth that
13 resulted from these enhancements is not clearly identified,
14 and further analysis of this would need to be performed in
15 light of the fact that the sponsors are going to be using
16 nomogram 2, which results in more undercorrections, which
17 may result in more enhancements, and then eventually may
18 result in more adverse events.

19 The loss of best spectacle acuity decreased
20 significantly in the patients as they were followed out to
21 six months in Group 1 that had LASIK only, and Group 1 that
22 had one LASIK-only enhancement, and they fell below the
23 guidance document.

24 ~~The flap dislocations in Group 2 decreased~~

1 because it appears that the surgeons developed evolving,
2 better techniques, the paintbrush technique to position the
3 flaps and viscous artificial tears, et cetera.

4 For efficacy, the sponsor intends to use only
5 nomogram 2 after approval.

6 Analysis of this PMA regarding safety and
7 efficacy is somewhat limited, due to the fact that the vast
8 majority of patients in Group 2 have been followed for only
9 three months. In addition, the data as submitted is
10 consistently to include all patients; i.e., those who were
11 undercorrected intentionally are combined with those in
12 whom emmetropia was the goal, and this may skew the data to
13 appear more negative regarding efficacy. Also, high
14 myopes, who were not able to achieve 20/20 vision, were
15 included in the data set.

16 An alternative way of presenting the data would
17 be to separate out patients who have been intentionally
18 undercorrected or present data that demonstrates the
19 attempted versus achieved correction, and stratify this
20 data by pre-op manifest refraction. This would allow a
21 patient and a surgeon to very easily extract data which
22 would be useful in predicting the outcome of an individual
23 patient, depending on their preoperative manifest
24 refraction.

1 In analyzing the efficacy of this nomogram and
2 the laser, it's important to consider the level of
3 training, qualifications, and supervision of the surgeons
4 who participated in this highly controlled trial, but
5 during the first 14 months of this trial, an average of 2.5
6 service calls were performed per month on the laser.
7 Thirty-five calls were made on the laser over 14 months.

8 Under these ideal conditions with ideal
9 surgeons and an ideal laser, the uncorrected vision after
10 last surgery in Group 1 was 87 percent were greater than or
11 equal to 20/40. In Group 2, 79 percent were greater than
12 or equal to 20/40. In the patients with primary LASIK
13 only, one procedure only, at six months 83 percent of them
14 were better than or equal to 20/40. In Group 2, 74 percent
15 were greater than or equal to 20/40 at three months,
16 because at six months there aren't enough patients to
17 evaluate.

18 As far as plus or minus a half diopter and plus
19 or minus 1.0 diopter, I'm not going to go through that,
20 because Malvina did a whole chart of that, but if you take
21 the numbers I just told you about the visual outcome of
22 20/40 and look at them a different way, which is saying
23 what are the chances of a patient not being 20/40 or better
24 after one procedure, if they're less than 7.0 diopters, it

1 seems 20 percent of them will not be 20/40 or better at
2 three months. In Group 2, it's 21 percent.

3 So another way of looking at this is that in
4 patients with a manifest refraction of less than -7.0, who
5 have just one LASIK procedure, their chance of having an
6 uncorrected visual acuity of less than 20/40 ranges between
7 16 and 29 percent. These numbers, from one procedure only
8 without enhancement, are significantly worse than those
9 published for surface PRK, but the sponsors pointed out
10 that you can do an enhancement and there's faster visual
11 recovery in patients who undergo LASIK, et cetera.

12 But does the procedure primarily provide a
13 faster visual rehabilitation in patients with a pre-op
14 manifest refraction less than -7.0? So, in one procedure,
15 are they really getting a better deal? The data doesn't
16 say so.

17 As far as sequential versus simultaneous
18 surgery, I believe that's a practice of medicine issue.

19 In summary, my review reveals significant
20 safety issues, primarily regarding the microkeratome, and
21 resultant complications, either device- or surgeon-related.
22 The steep learning curve is apparent, even in the hands of
23 the most experienced of surgeons, and the incidence of
24 epithelial ingrowth with repeated enhancements remains

1 unresolved.

2 The efficacy of this procedure does demonstrate
3 faster visual recovery than PRK and a significant reduction
4 in myopia. However, a significant number of patients
5 require one to two enhancement procedures. In patients
6 that are less than 7.0 diopters, the primary results --
7 primary being one LASIK -- do not appear to be as good as
8 those seen with surface PRK, and this raises an issue of
9 approval of this device for patients with less than -7.0
10 diopters myopia, unless they're planning on having more
11 than one procedure.

12 There are some additional data which would
13 allow for better analysis of this PMA. These are as
14 follows. I'll list them for you. One, stratification of
15 the data by preoperative manifest refraction to demonstrate
16 the attempted versus achieved correction, thereby
17 eliminating the negative overall effect of patients who
18 were treated for monovision or high myopes who may not
19 achieve 20/20 vision.

20 Two, the rate of adverse events and epithelial
21 ingrowth directly attributable to the enhancement
22 procedures and repeated enhancement procedures.

23 Three, further explanation of the large number
24 of service calls made on the laser, 2.5 calls per month.

1 Four, I need some clarification of the contrast
2 sensitivity data and this loss of best spectacle corrected
3 visual acuity with the BAT testing in Group 1, but not
4 Group 2. I didn't quite understand that.

5 Next, why are you requesting the single zone
6 for patients less than -7.0 diopters if the multizone in
7 the first three volumes showed a mean undercorrection of
8 only minus a half and the single zone showed a mean
9 undercorrection of -0.7? The multizone appeared to produce
10 more correction than the single zone, so why are you just
11 asking for single zone in -7.0? And in Group 2, were the
12 patients less than 7.0 diopters treated with multizone or
13 single zone? That wasn't clear to me.

14 The last thing that needs to be clarified to me
15 is in Dr. Thompson's kind of rehashing of the data, looking
16 at how it compared to Summit, VISX, and the guidance
17 document, the Ns changed. You have an N of 218 at six
18 months in some of your slides, and an N of 302 at six
19 months in some of your slides, and the same thing with the
20 12-month slides. But the N of 302 is considerably less
21 than the N of how many patients were examined at six
22 months. Four-hundred and twenty-three patients were
23 examined at six months of Group 1 and 22 patients of Group
24 ~~2 were examined at six months, so why do these Ns keep~~

1 changing? It might be really obvious. I just didn't get
2 it.

3 In summary, finally, I just have one comment,
4 and this is a concern I have about LASIK. It may indeed be
5 better than surface PRK for -7.0 diopters, and it certainly
6 seems to be better than anything else we have to offer
7 patients who are greater than -7.0 diopters, but be careful
8 about trying to convince people that it's faster recovery
9 and less pain, because if you have to have all these
10 enhancements and we don't know the complication rates of
11 all these enhancements, it's like trying to convince people
12 that fast food is of equal nutritional value to salad,
13 baked potato, and a piece of baked chicken. It's just not,
14 and the public needs to understand it's not a drive-through
15 procedure.

16 I'm done.

17 DR. McCULLEY: To clarify procedure, what we're
18 going to do is invite the sponsor back to the table to
19 respond to questions asked directly of them by the panel
20 members, and we will start off by asking those who were
21 primary reviewers to pose their questions to you for your
22 response. As I understand it, this is a time for response
23 to questions from panel, not specifically a time to expand
24 presentation or rebut issues. Based on that, I would like

1 to invite you back to the table.

2 Dr. Van Meter was the first reviewer and had
3 some specific questions. I am going to turn the floor to
4 him now to ask his questions.

5 DR. VAN METER: I will repeat the questions
6 that I had at the end of my review. Number one is why does
7 the denominator go down in your --

8 DR. THOMPSON: Can we wait just one second
9 until we get set up?

10 MS. THORNTON: Excuse me. Do you need to wait
11 until Dr. Waring returns as well?

12 DR. THOMPSON: We would like that, and if we
13 could get an overhead projector set up, that would be
14 helpful.

15 DR. HIGGINBOTHAM: Mr. Chair, can we take a 10-
16 minute break while they're getting set?

17 DR. McCULLEY: While we're setting up, why
18 don't we take a 10-minute recess?

19 (Recess.)

20 DR. McCULLEY: If we can reconvene the
21 discussions, I will restate, the sponsor has been invited
22 to return to the table to respond directly to questions
23 posed to them by panel. My suggestion is that we start
24 with the primary reviewers asking their questions first, if

1 that meets with panel agreement.

2 Dr. Van Meter?

3 DR. VAN METER: Dr. Waring, am I correct in
4 assuming that the only difference between Group 1 and Group
5 2 is that the nomogram was adjusted for more
6 undercorrection, and there should be no difference in
7 attempted and achieved data between Group 1 and Group 2?

8 DR. WARING: This is Dr. Waring. Yes, Dr. Van
9 Meter, that's correct, and I think it's very important, as
10 the panel tries to unravel Group 1 versus Group 2, that you
11 realize that the surgical technique was absolutely the
12 same, entry criteria absolutely the same, follow-up
13 absolutely the same. The only difference was that we took
14 the nomogram and shifted it in what we thought was a more
15 conservative direction to reduce the number of
16 overcorrections, which we did by 50 percent. So questions
17 of safety, stability, should be exactly the same for Group
18 1 as Group 2.

19 DR. VAN METER: Thank you.

20 Dr. Thompson, this is the slide I was referring
21 to earlier. I just couldn't help but notice, over the last
22 three intervals, that the denominator goes down, and is
23 this a reflection on your entry of patients into the study
24 ~~or the incidence of LASIK being performed at the Emory~~

1 Vision Correction Center?

2 DR. THOMPSON: This is Dr. Thompson. As I
3 recall, what was happening here, the reason the
4 denominator's going down, is that enrollment in Group 1 was
5 being completed and Group 2 was being started, and that's
6 why the overall denominator is decreased here. Again,
7 these are Group 1 eyes, okay? So that's why there's the
8 denominator, but we did want to show the overall incidence
9 of complications, which as a percentage continues to
10 decline throughout the time that the surgery was performed.

11 DR. VAN METER: Thank you.

12 Could you please provide some more information
13 on what happened to the 10 percent of subjects that by
14 survey were not satisfied at the end of one year?

15 DR. WARING: No. The reason that we did not
16 provide the questionnaire data to the panel is that it's
17 simply very incomplete. These will be administered at 12
18 months and we're waiting for those exit interviews. We did
19 present the results of the two questions that I thought
20 were important. That is, distance spectacle wearing and
21 overall satisfaction on the roughly 200 patients that we
22 had who exited the trial, but we have done no careful
23 analysis of that and we don't even know that the 10 percent
24 figure will reflect 1,000 eyes. Right now, it's only 200.

1 DR. VAN METER: Finally, were there any
2 complications due to enhancement procedures?

3 DR. THOMPSON: The question is complications
4 following enhancements. I think we have some analysis of
5 that. This slide shows the percentage of patients losing
6 two lines or more of best spectacle corrected acuity after
7 enhancement for Group 1 data, and this is after enhancement
8 only.

9 DR. VAN METER: What sort of things would
10 happen to make -- would this be astigmatism or flap
11 complications?

12 DR. WARING: Well, let me address that. As you
13 saw from the videos the enhancement procedure is
14 technically much easier than the primary procedure, because
15 it does not involve a microkeratome. You do have to lift
16 the flap, but breaking the edge of the wound and folding
17 the flap back is a very easy thing to do, and although I'd
18 have to go look specifically to document this statement,
19 I'm not aware of flap complications per se that occurred
20 intraoperatively as a part of the enhancement procedures.

21 Now, postoperatively, you can have epithelial
22 ingrowth. You can have flap slip. You can have anything
23 after an enhancement that you can have after a primary
24 procedure, because the flap is functioning just about the

1 same, but globally speaking, an enhancement procedure is a
2 much safer procedure than the primary procedure.

3 DR. McCULLEY: I think the question is do you
4 have data on the complication rate with enhancements? Do
5 you have an initial complication rate with the procedure?
6 What additional additive complications are associated with
7 each enhancement procedure?

8 DR. WARING: I have to ask my colleagues.
9 Excuse me. Wendy, do we have a page on that?

10 No, those data are available. That is, we make
11 all of our entries afterwards, and it looks like we did not
12 present that specific piece of information to the panel.
13 That can be done.

14 DR. THOMPSON: I think the best we have is
15 shown on this slide, which is again the percentage of
16 patients that did have enhancement and those losing two
17 lines or more. There are no primary eyes in this data.

18 DR. VAN METER: The X axis there, does that
19 mean enhancements that happened within three months of
20 initial surgery?

21 DR. THOMPSON: Three months following
22 enhancements.

23 DR. VAN METER: Following the enhancement
24 procedure. So since some patients had two or maybe three

1 enhancement procedures --

2 DR. SUGAR: There are no Ns in that, so those
3 aren't necessarily the same patients, correct? Some
4 patients were followed longer and some weren't, or did all
5 patients --

6 DR. THOMPSON: That's correct. That's on all
7 patients.

8 DR. VAN METER: Thank you, Dr. Thompson.

9 My last question is could you address the 8
10 percent loss of two or more lines of best spectacle
11 corrected acuity in the subset of patients over 7.0
12 diopters?

13 DR. THOMPSON: Yes. That's shown for you on
14 this slide, and again, this analysis was not submitted to
15 the panel or to FDA prior to this meeting, and we apologize
16 for that. We just simply didn't complete it in time to get
17 it out to you.

18 This shows that, looking at this subset, 8
19 percent lost two lines or more of best spectacle corrected
20 acuity if you look only at the greater than 7.0 subgroup.
21 I think it's very important to keep in mind what's
22 available in terms of alternative treatments. That's
23 what's the intent of this slide.

24 ~~We think that the mechanism for most of these~~

1 patients is mild degrees of irregular astigmatism. That
2 was more likely to be seen. It was our impression it was
3 more likely to be seen in patients with higher degrees of
4 correction than in lower degrees. The numbers reflect
5 that.

6 DR. WARING: And this is why we proposed,
7 instead of the range of 7.0 to 22.0, a cutoff in labeling
8 of -15.0. We think that's safer for the patients.

9 DR. VAN METER: If you eliminated those
10 patients that had 15.0 to 22.0 diopters, would this data
11 --is it your impression that the patients that comprised
12 that 8 percent were predominately those between 15.0 and
13 22.0 diopters?

14 DR. WARING: That's my opinion. I'd have to
15 look carefully to see if we can prove it.

16 DR. McCULLEY: I misunderstood then. I thought
17 the data you were presenting were on patients up to 15.0.

18 DR. WARING: That is incorrect. The data that
19 we presented is the entire cohort that we did up to 22.0
20 diopters, no patients omitted.

21 DR. McCULLEY: And how many patients were above
22 15.0? A small number?

23 DR. WARING: It represents roughly 5 percent.
24 It's a small percentage.

1 DR. VAN METER: So it's that patient population
2 between 15.0 and 22.0 that skews this.

3 DR. THOMPSON: We think so. We'd have to do an
4 independent analysis of it for that.

5 DR. WARING: We don't have those numbers, Dr.
6 Van Meter.

7 DR. VAN METER: Thank you.

8 DR. McCULLEY: Dr. Sugar?

9 DR. SUGAR: In terms of complications, you
10 reported 20 eyes requiring reoperation because of
11 epithelial ingrowth in Group 1 and three in Group 2. You
12 may have presented subsequent data to us, but this was in
13 our first package with the first couple of amendments.
14 Have there been subsequent needs for epithelial scraping?

15 DR. WARING: Dr. Sugar, this is Dr. Waring.
16 With your permission, since so many questions have come up
17 about epithelial ingrowth, I would like to take a moment to
18 present a view of specifically our management and the
19 factors affecting epithelial ingrowth, which hopefully
20 would address questions previously asked by Dr. Macsai and
21 others. Would that be okay? It would be about 10 slides.

22 DR. SUGAR: That's up to Jim.

23 DR. MACSAI: Is this new data?

24 DR. WARING: No.

1 DR. MACSAI: What is it?

2 DR. WARING: This is a digest of information
3 that's in the PMA, but it addresses specifically how we
4 managed epithelial ingrowth, the factors that we thought
5 affected it, the response to your questions, what factors
6 are affecting epithelial ingrowth, the response to Dr.
7 Sugar's question --

8 DR. SUGAR: My question is really more what is
9 the incidence or the cumulative frequency of the
10 complication.

11 DR. WARING: Yes, we can address that, and if
12 you'll allow me to ask Dr. Carr to present this sequence,
13 this subanalysis of epithelial ingrowth, we can answer your
14 question about whether or not it's ongoing, Dr. Sugar.

15 DR. McCULLEY: Just to be certain, you must do
16 this to answer his question? You cannot answer his
17 question directly? You have to give a 10-slide
18 presentation?

19 DR. WARING: The answer to this question is in
20 these slides, and I do not know the answer off the top of
21 my head. That is, whether or not the incidence went up.

22 DR. McCULLEY: Then would you like to --

23 DR. SUGAR: Please.

24 DR. McCULLEY: Okay. Then, please do.

1 DR. CARR: My name is Jonathan Carr from Emory
2 University. I'll briefly go through the earlier slides to
3 get to the answer.

4 DR. MACSAI: Could you speak louder, sir?

5 DR. CARR: I'll go through the earlier slides
6 to get you to where you need to be. This is a separate
7 analysis of those eyes that had epithelial ingrowth in
8 Group 1, and we performed two separate multiple logistic
9 regression analyses. These are the two outcomes we sought
10 to answer. Question 1 was other risk factors that we can
11 identify for epithelial ingrowth of any description beneath
12 the flap, and the second analysis, which I'll jump to
13 immediately, is are there any risk factors predictive of
14 epithelial ingrowth progressing to a flap revision?

15 These were test variables, enhancement versus
16 primary LASIK on the left, surgeon experience, the
17 incidence of flap complications, postoperative epithelial
18 defects, which have been implicated, and the occurrence of
19 ARC-T microperforations in the stromal bed beneath the
20 flap.

21 Going straight to the results, for the
22 epithelium of any description beneath the flap, many of
23 these just did not require flap revision. These were the
24 significant variables, and I have calculated an odds ratio

1 for you. Epithelial defects postoperatively within 24
2 hours had an increased risk. The odds ratio there means
3 that the increased risk is 30 percent compared to not
4 having an epithelial defect, controlling for all other
5 variables. Similarly, enhancement carries a 10 percent
6 increased risk of any epithelium compared to not having an
7 enhancement.

8 Surgeon experience was protective. The three
9 surgeons in the study with previous lamellar surgery
10 experience had a 10 percent lower chance of getting
11 epithelium beneath the flap compared to them not performing
12 the surgeries. Postoperative flap slippage in the first 24
13 hours and arcuate transverse keratotomy microperforation
14 also carried with them a 10 percent increased risk of any
15 epithelium.

16 But the question you're more interested in is
17 which factors predicted flap revision? The only two we
18 were able to implicate with 90 percent accountability were
19 epithelial defect postoperatively, which in this situation
20 carries a 60 percent increased risk of a flap revision,
21 compared to not having an epithelial defect. These are
22 only where the endpoint is a flap revision. We're only
23 looking at a small number of eyes here. Arcuate transverse
24 keratotomy producing microperforation at the time of LASIK

1 also had a slightly increased risk.

2 I'm going to progress to this slide which shows
3 that during the study, by quarter, the incidence of
4 epithelium of any description beneath the flap decreased,
5 and this is only the inexperienced surgeons at the time of
6 entry into the study. The three previously experienced
7 lamellar surgeons have not been represented here in order
8 to demonstrate to you that the incidence of epithelium
9 beneath the flap of any description decreases with time.

10 DR. WARING: What was the role, Dr. Carr, of
11 time? The question Dr. Sugar asked was did the
12 epithelium --

13 DR. McCULLEY: Dr. Waring? Please, point of
14 order.

15 Dr. Sugar?

16 DR. SUGAR: That's appropriate. Marian asked
17 the question of does epithelium creep in over time, and
18 does the frequency in Group 1, which is frozen in terms of
19 patient entry, does the frequency of the occurrence go up
20 over time, or do you see all your epithelial ingrowths in X
21 months, and what is that time?

22 DR. CARR: I think these data support the
23 occurrence of epithelium in the immediate period following
24 ~~surgery as a result of intraoperative events or post~~

1 operative events. The fact that these variables all occur
2 at that time, within 24 hours of surgery, means that it is
3 unlikely, in our opinion, that epithelium would seed
4 beneath the flap or begin to proliferate beneath the flap
5 at any time subsequently without it being evident to the
6 surgeon at prior postoperative visits.

7 DR. RUIZ: What is an epithelial defect, since
8 you're cutting through the epithelium?

9 DR. CARR: Epithelial defects -- let me explain
10 that many of these variables, such as epithelial defect,
11 flap slippage, and ARC-T microperforation, produce a
12 relative edema in the flap in the early postoperative
13 period. What that does is it increases the likelihood of
14 the edge of the flap failing to adhere as it would
15 otherwise do. The next point to make about that is that
16 the epithelial defects can even occur in the center of the
17 flap. They do not have to occur, based on our analysis, at
18 the edge of the flap, and that supports the edema theory.

19 DR. RUIZ: But every single one of these have
20 epithelial defects. What is your definition as presented
21 here?

22 DR. CARR: I'm sorry, I didn't understand.

23 DR. RUIZ: Well, every one of them have
24 epithelial defects since you're cutting through the

1 epithelium.

2 DR. CARR: Oh, okay. I agree, there is a small
3 defect where the keratome blade breeches the cornea to
4 create the flap. The point I was trying to make was that
5 under normal circumstances, in the absence of anything that
6 produces relative flap edema, that is not a problem. So
7 epithelial cells that may choose to fill in this very small
8 defect coming from the limbus do not, in error so to speak,
9 get beneath the flap, because there is no flap edema.

10 DR. RUIZ: So how do you define an epithelial
11 defect?

12 DR. THOMPSON: This is Dr. Thompson. Let me
13 try to respond to Dr. Ruiz' question. Normally, at 24
14 hours, there is no epithelial defect. It's closed. If you
15 put fluorescein in the eye, there's no stain. There are
16 occasions that occur both during primary cases when the
17 microkeratome translates across the eye and creates a
18 separate defect apart from the wound, some epithelium gets
19 scraped off, or when you're doing an enhancement. You saw
20 the video of the enhancement. When you go around the edge
21 with the hook, some areas may get pulled off. That's what
22 we define as an epithelial defect apart from the wound.

23 DR. RUIZ: Thank you.

24 DR. McCULLEY: Dr. Macsai?

1 DR. MACSAI: Can I proceed?

2 DR. McCULLEY: On this issue, yes.

3 DR. MACSAI: This is Dr. Macsai. The question
4 about the epithelial ingrowth that I have is perhaps
5 misunderstood. I assume, and perhaps wrongly, that at 24
6 hours you might see a small seed of epithelium under the
7 flap -- not Grade 3 at 24 hours, but at 24 hours it's a
8 small seed. Over time, this increases in size. There is
9 some, indeed, proliferation of epithelium between the flap
10 and the stromal base, and then eventually that requires
11 removal either due to obstruction of the visual axis or
12 resultant irregular astigmatism.

13 So if there is any epithelium between the two
14 stromal surfaces, it seems to me there's a potential for
15 it, over time, to increase. Does that happen? Are you
16 longitudinally following patients either after primary
17 procedure or after enhancement procedure?

18 DR. THOMPSON: This is Dr. Thompson. Let me
19 address the first component of your concern the best I can.
20 It's been our observation that for epithelial ingrowth to
21 progress and be problematic -- i.e., encroach on the visual
22 axis, cause irregular astigmatism -- it has to be
23 contiguous with the epithelium at the edge of the wound.

24 ~~Isolated nests of epithelial cells entrapped in the~~

1 interface probably at the time of the primary surgery or at
2 the enhancement are rarely observed to cause problems.

3 As I understand your question, the second
4 question is what longitudinally is the timeframe to observe
5 problems from epithelial ingrowth? The data is in there.
6 We could probably go back and look at a longitudinal
7 analysis of it. I don't believe we've conducted that yet.
8 It's our clinical impression that those are detected early,
9 two weeks to a month after either the primary procedure or
10 the enhancement surgery. Again, a continuous sheet of
11 epithelium to the edge is necessary to cause problems in
12 our experience.

13 Does that answer your question?

14 DR. MACSAI: Yes. But so far, Dr. Thompson,
15 you don't have, right there on the computer, that
16 longitudinal analysis?

17 DR. THOMPSON: This is Dr. Thompson. We
18 haven't performed that to my knowledge yet.

19 DR. MACSAI: Because what I'm interested in is
20 not only after the primary procedure, but with what Dr.
21 Carr said, with a 10 percent increase with enhancement, and
22 then is that another 10 percent with the second
23 enhancement. What is the longitudinal natural course with
24 one or two enhancements? In other words, will a patient

1 who needs one enhancement -- so that's two surgeries --
2 then need a third one to get epithelium removed? That's
3 what I'm trying to figure out.

4 DR. THOMPSON: I understand. We would have to
5 perform that.

6 DR. McCULLEY: Thank you.

7 Dr. Sugar?

8 DR. SUGAR: Two other non-related issues that I
9 brought up in my discussion before. One is how do you
10 inform patients and how do you recommend, once this is
11 done, I presume at other sites, that patients and surgeons
12 be informed of the high frequency of the need for
13 enhancements?

14 The other question is how do you intend to
15 certify that surgeons are qualified to do the procedure?

16 DR. WARING: This is George Waring. To answer
17 your first question, 100 percent of patients are told that
18 they have a chance of an enhancement. The figure I usually
19 quote is 30 percent, but I don't present it to them as a
20 statistic. I present it to them as a likelihood. Dr.
21 Macsai's comments were very much to the point in her
22 review, that this is presented to the patient as a multi-
23 stage procedure, to the point that patients will come back
24 postop and say, "Dr. Waring, I think I need an enhancement

1 in my right eye." So it is not presented at all as a one-
2 step procedure but as a formally staged procedure; and the
3 patients, incidentally, are not charged for the
4 enhancement. It's part of the procedure itself.

5 Does that answer that question?

6 DR. SUGAR: Yes.

7 DR. WARING: Our efforts to train surgeons in
8 the Emory LASIK technique go along the lines that we had in
9 our initial PMA. We have outlined our 10-step training
10 program there. It's not categorically different from the
11 way we do skills transfer in any other part of
12 ophthalmology. The surgeons are expected to read first.
13 They're given a written test before they're allowed to
14 participate in anything else, and they have to pass that
15 test at an 85 percent level. That's followed by a
16 laboratory hands-on skills transfer session with a
17 microkeratome, animal eyes, formal practice and education
18 there. That's followed by the observation of videotapes
19 and observation of live surgery in the hands of a skilled
20 surgeon, which then, at that surgeon's discretion, is
21 followed by more practice or not.

22 That surgeon then selects patients from their
23 practice, their own private patients, to bring in for their
24 initial procedure, which is monitored; that is, a skilled

1 surgeon on our staff is present as a first assistant to
2 help them through those initial cases. We have eight eyes,
3 four patients that were required for that, and we have a
4 formal two-page checklist that we go down and we review
5 with the surgeon after each case. So we say, "We think you
6 did great on this but not great on that," and at the
7 conclusion of that series of eyes, then the surgeon is
8 either passed or not passed in terms of being allowed to
9 bring cases to the center.

10 DR. McCULLEY: This presumably would be part of
11 your labeling of your proposal that you just outlined?

12 DR. WARING: We would propose that. It would
13 be at the discretion of the agency how the final labeling
14 is done.

15 DR. SUGAR: This may be naive, but in order for
16 a new site to use your technology, how will you assure that
17 this is carried out? That is, are you going to be
18 available? Are you going to provide courses? This is a
19 practice of medicine issue now, so people can do it anyway.

20 DR. WARING: This is George Waring. For people
21 to use the Emory System, they would have to be trained in
22 the outline that I've told you. I myself might not train
23 all of those surgeons, but we would provide a skilled
24 surgeon to assist with that training, and the steps that I

1 just outlined for you would be implemented at any site
2 prior to their being able to use the Emory System.

3 DR. SUGAR: Thank you.

4 DR. McCULLEY: Does that answer all of your
5 questions, Dr. Sugar?

6 DR. SUGAR: Yes.

7 DR. McCULLEY: Dr. Macsai?

8 DR. MACSAI: This is Dr. Macsai. I'm not sure
9 that some of my questions can be answered without some
10 further analysis of data, such as the attempted versus
11 achieved. You don't have that right here, do you?

12 DR. THOMPSON: This is Dr. Thompson. Could you
13 restate your question again so I can see if we do have it?

14 DR. MACSAI: I wanted to see stratification of
15 data by preop manifest refraction to demonstrate the
16 attempted versus achieved correction, eliminating the
17 negative overall effects of patients who are treated for
18 monovision or high myopes who may not be able to achieve
19 20/20 or 20/40 vision.

20 DR. THOMPSON: This is Dr. Thompson. We have
21 not completed that analysis yet. We would have to do that.

22 DR. MACSAI: Okay. I guess my second question
23 you also haven't completed yet, which is the epithelial
24 ~~ingrowth related to the enhancement procedures.~~

1 The third question then is explanation of the
2 large number of service calls made on the laser, and also
3 I'd like some clarification about the microkeratome. Did I
4 understand correctly that you have two microkeratomes that
5 you used? They're the same one, but you have two of them
6 that the surgeons used? And how often were those serviced?
7 Because there seems to have been some problems in the past
8 with microkeratomes.

9 DR. THOMPSON: This is Dr. Thompson. Your
10 first question related to the laser. We did have a high
11 number of service calls, and the specifics were provided to
12 you in the submissions. The explanation for that I think
13 lies in the fact that we had had one of the original Summit
14 lasers at Emory for many years. In fact, Maureen O'Connell
15 is here from Summit. I think it was originally installed
16 in 1989 or 1990. We call it the Model T laser. So it had
17 been around for some time and we had put a lot of use on
18 it. We think that that use is related to the high
19 frequency of service problems.

20 I will add that it was later determined by
21 Summit service personnel that there was a slow leak in the
22 laser cavity. They replaced the laser cavity for us
23 probably about six months ago, and since that has been done
24 ~~the service call frequency has gone way down, a fraction of~~

1 what it was before. So we think it was related to that.

2 DR. WARING: Let me emphasize that we put 1.2
3 million shots on that laser before the new cavity. It's
4 the busiest Summit laser in the United States. Our service
5 representative lived in Atlanta, so we had a preventive
6 maintenance program where he came by on a regular basis,
7 which we counted in those numbers that we put in there.
8 Because our laser was used more heavily than any other one
9 in the U.S., we insisted on a lot of service calls.

10 DR. MACSAI: Of course, my concern would be the
11 laser that's not used as much as yours where perhaps it's
12 not serviced as much. Does it need to be serviced as much
13 to get as good results? That's what I'm trying to figure
14 out.

15 DR. THOMPSON: This is Dr. Thompson. It's very
16 important that the user follow the manufacturer's
17 recommendation for calibration procedures, which was done
18 every day before use. As long as that is followed, then we
19 think it's safe for use. It meets its specifications.

20 DR. MACSAI: Can you expand on the
21 microkeratomes?

22 DR. THOMPSON: Yes. We used two different
23 microkeratomes. The numbers of the microkeratomes
24 corresponded to the numbers that the manufacturer has

1 created. It's my understanding that 241 and 626 were the
2 two microkeratomes that we used. They were slightly
3 different models but the same basic design was used.

4 DR. MACSAI: Did 241 have more free flaps than
5 626, or anything like that?

6 DR. THOMPSON: That's a very good question. We
7 haven't gone back and analyzed independently if there was
8 any difference. It's our clinical impression that, no, you
9 were just as likely to have a flap complication with 626 as
10 with 241. We didn't notice that.

11 I would also like to add that we have also
12 gotten on a program of routine maintenance with the
13 microkeratomes that's kept both in excellent working
14 condition.

15 DR. MACSAI: How frequent is routine
16 maintenance?

17 DR. THOMPSON: About once every six weeks.

18 DR. McCULLEY: And what does that mean? You
19 send it in, or they come?

20 DR. THOMPSON: We send it back and it's checked
21 and calibrated and sent back to us.

22 DR. MACSAI: In Group 2, were the patients who
23 were less than -7.0 treated with the multizone or the
24 single zone profile?

1 DR. WARING: The single zone versus multizone
2 in the primary PMA in the Group 1 was --

3 DR. MACSAI: I was asking about Group 2.

4 DR. WARING: Oh, I'm sorry. In Group 2 it was
5 single zone under -7.0 for all eyes.

6 DR. MACSAI: Okay. Can you just tell me,
7 because I'm curious, why that's better in your opinion, Dr.
8 Waring, for patients less than 7.0 than the multizone?
9 Because in the Group 1, it looked like the multizone was
10 better.

11 DR. WARING: The reason in Group 1 that we
12 compared single zone to multizone under 7.0 was to figure
13 out what's the difference. When we looked at topography
14 and other outcomes -- and, if you wish, we have a formal
15 analysis of that -- we didn't see any difference, except
16 that the multizone had a different effect. It was a matter
17 of dosing rather than a qualitative difference in the two.
18 At that point, we stopped that part of the trial. For
19 Group 2, they started before we had completed that
20 analysis, and we said let's just keep it simple, let's do
21 single zone for everybody in Group 2.

22 So we did not conclude that single zone or
23 multizone was better under 7.0 diopters; there's just a
24 little difference. If you change the calibration on

1 multizone and just move it up to do single zone, they turn
2 out the same.

3 DR. MACSAI: Okay.

4 DR. WARING: If you want more data, we have
5 that.

6 DR. MACSAI: I just was curious because it was
7 in Group 1.

8 I just have another technical question to you.
9 How do you enhance when you have a loose flap? No hinge,
10 completely cut off, the flap. A free flap.

11 DR. WARING: When you have a free disk, a total
12 disk or a cap has been cut and there is no hinge, and then
13 you want to go back and enhance, you break open the edges
14 we showed 270 degrees, you leave the edge attached, there's
15 a scar there and you leave that attached, you fold it back
16 and it functions as a hinge, it does not come off. You
17 ablate and you put it back down.

18 DR. MACSAI: Okay. Do you have an analysis of
19 the Group 2 incidence of intraoperative complications?

20 DR. THOMPSON: This is Dr. Thompson. We
21 haven't looked at complications stratified between Group 1
22 and Group 2. All were included for the analysis.

23 You mean longitudinally?

24 DR. MACSAI: Longitudinally and latitudinally.

1 DR. THOMPSON: In terms of preparing the
2 incidence between Group 1 and Group 2?

3 DR. MACSAI: Yes, but also the incidence of
4 buttonholes and free caps in Group 2.

5 DR. THOMPSON: We haven't made that analysis
6 comparing Group 1 and Group 2 for intraoperative
7 complications.

8 DR. MACSAI: Because there's this implication
9 that they're going to go down.

10 DR. THOMPSON: The only difference between
11 Group 1 and Group 2 was the laser software. There's no
12 difference of anything else done in the operating room --

13 DR. MACSAI: No -- surgeon experience.

14 DR. THOMPSON: Yes, surgeon experience. At the
15 time we did Group 2, we had more experience. So that would
16 be found on that first table that we showed, the bar chart
17 showing complications decreasing with time.

18 DR. MACSAI: But you said the bar chart that
19 you showed was only Group 1 data.

20 DR. THOMPSON: That's correct.

21 DR. MACSAI: So is it substantiated by Group 2
22 data? That's my question.

23 DR. WARING: We don't have those numbers.

24 DR. MACSAI: Okay. I guess maybe we'll do this

1 later in discussion, but the contrast sensitivity data
2 looks kind of confusing to me, as in why the loss of best
3 spectacle corrected visual acuity with the BAT is higher in
4 Group 1 than Group 2. I don't understand that.

5 DR. WARING: Neither do I, and I don't make
6 that comment sarcastically.

7 DR. MACSAI: What do you mean?

8 DR. WARING: Well, in our primary submission we
9 did not submit the contrast sensitivity data because we
10 didn't know how to interpret it. It's a complex
11 interpretation. The agency asked us, then, to submit those
12 data, and so we submitted them. We laid them out in as
13 clear a way as we could understand, which was the gain and
14 loss slide that I showed you before. The fact that there
15 are different patterns at different spatial frequencies,
16 the fact that they go in both directions makes it difficult
17 to interpret.

18 Now, I am not a contrast sensitivity expert and
19 maybe someone on the panel could comment, but the
20 discussions I've heard among erudite lab workers and
21 clinicians usually end up with, "Yes, we think contrast is
22 very important, but we don't know quite how to interpret
23 it." This is our conclusion. This particular slide
24 ~~showing different patterns at different spatial~~

1 frequencies, and both losses and gains don't lead to any
2 outcome patterns that I can apply clinically to help me
3 interpret safety.

4 DR. McCULLEY: Dr. Rosenthal?

5 DR. ROSENTHAL: Just to clarify the issue of
6 why it was requested is because it's requested of all
7 people doing PMAs on laser refractive surgery. Though
8 there is some uncertainty as to its role, there are
9 certainly some issues which have been well defined which
10 could affect contrast sensitivity, and hence issues of
11 vision under low light conditions.

12 DR. MACSAI: Right.

13 DR. McCULLEY: Dr. Drum?

14 DR. DRUM: If I could just make a very brief
15 comment about the increases and decreases. If you take any
16 data set that has a distribution, you can provide the same
17 analysis and you'll get increases and decreases.

18 DR. McCULLEY: Speak up, please.

19 DR. DRUM: If you take any data set that has a
20 distribution of values, you can do that same type of
21 analysis and you will get increases and decreases. That's
22 not anything special with regard to this type of data.
23 It's just that it's interesting and informative to see
24 whether the decreases are predominant or the increases are

1 predominant. It's also of interest eventually in the
2 labeling. We're interested in seeing what happens to
3 individuals, as opposed to seeing what happens to the mean
4 of the distribution.

5 DR. McCULLEY: You've had a chance to look at
6 their data?

7 DR. DRUM: Yes. Well, we've had a chance to
8 look at their contrast sensitivity data.

9 DR. McCULLEY: That was the question. Prior to
10 this meeting?

11 DR. DRUM: Right.

12 DR. McCULLEY: And, as I understand it, the
13 sponsor is not certain how to interpret it. I guess my
14 question to you would be, can you shed any light on an
15 interpretation?

16 DR. DRUM: I think the suggestion that Dr.
17 Waring made is reasonable, that at least some of the
18 spatial frequency-specific effects may be related to
19 magnification differences. If the entire curve is shifted
20 because the image is larger after surgery, you could
21 predict qualitative changes like that. But I don't know if
22 that explanation can account for all the changes or not.

23 DR. McCULLEY: Dr. Bullimore?

24 DR. BULLIMORE: While we've got this up, let's

1 put it in context. I believe this is the vector vision
2 chart?

3 DR. WARING: That's correct, the sine-wave
4 gradient vector vision chart.

5 DR. BULLIMORE: When you're talking about
6 losses of two lines or two test increments, I believe each
7 test increment corresponds to 0.15 of a log unit. Is that
8 correct?

9 DR. WARING: That's correct.

10 DR. BULLIMORE: So what we're looking at here
11 is the number of patients who either gained or lost 0.3 log
12 units of contrast sensitivity. If you want to equate that
13 to visual acuity, and I hesitate to do that, 0.3 log units
14 is three lines on the chart. It's therefore particularly
15 worrying that we see not only substantial numbers of
16 patients who lose that amount of contrast sensitivity, but
17 also those that gain contrast sensitivity.

18 This could indicate a number of things. It
19 could indicate, for example, the inherent variability of
20 this particular test. This is not a letter chart test. It
21 has some reported repeatability in the literature, and it
22 may just be messy data. That's not meant to characterize
23 the investigators; it's meant to characterize the
24 ~~investigators and/or the test that they chose to use.~~

1 It is, however, worrying, and I think this is
2 what Dr. Drum is speaking to, that for the lowest spatial
3 frequency, over 25 percent of patients lost 0.3 log units
4 of contrast sensitivity. That's not an insignificant
5 concern. Yes, that's offset by the 14 percent that gained
6 0.3 log units, but I think it's something that we may need
7 to address -- maybe not at this stage but at the labeling
8 stage, given that the only data we have to go on is the
9 data that the sponsor has collected.

10 DR. McCULLEY: Any other comments about
11 contrast sensitivity?

12 DR. MACSAI: Can I ask for clarification about
13 the BAT testing?

14 DR. McCULLEY: I suppose so.

15 (Laughter.)

16 DR. MACSAI: Thank you.

17 I didn't understand why there was loss of best
18 spectacle corrected visual acuity with BAT testing in Group
19 1 but not in Group 2.

20 DR. WARING: I don't know.

21 DR. BULLIMORE: Is this data that's been
22 submitted that we should be referring to, Dr. Eydelman?

23 DR. EYDELMAN: My review of Amendments 4 and 5
24 address that on page 10 and 11.

1 DR. McCULLEY: Thank you.

2 DR. WARING: This is Dr. Waring. Dr. Macsai,
3 if I had to try to help you understand that, and ourselves
4 as well, I think I would just say that in Group 2 there's a
5 relatively smaller number of eyes followed after three
6 months, and that's what these data reflect. It may simply
7 be a sampling problem. We just don't have enough eyes out
8 there after three months in Group 2 to make meaningful
9 judgments and comparisons, and this is why we have not
10 spent a lot of time presenting our Group 2 data, because
11 the follow-up is short.

12 DR. MACSAI: Okay. Well, do you know in Group
13 1 if the patients who did lose acuity with BAT testing, are
14 they patients who complained of glare? And did the
15 patients who got this 27 percent loss at cycle 3, did they
16 complain of problems with low contrast situations?

17 DR. WARING: We do not have in any of our
18 testing psychometric data relating to glare. One of the
19 reviewers commented on quality of life data previously, and
20 we do not have any data on quality of life. That's not
21 part of this trial.

22 DR. MACSAI: It's not part of the trial because
23 you haven't gotten it back yet at 12 months?

24 DR. WARING: No. We have no data, no

1 questions, no efforts to gather subjective glare and
2 quality of life data.

3 DR. MACSAI: What about halos?

4 DR. WARING: Or halos.

5 DR. MACSAI: Or difficulty driving at night?

6 DR. WARING: Or difficulty driving at night.

7 DR. HIGGINBOTHAM: Dr. Chair, I have a question
8 about that.

9 DR. McCULLEY: Okay.

10 DR. HIGGINBOTHAM: What are you asking the
11 patients to assess patient satisfaction?

12 DR. WARING: In the 12-month questionnaire --
13 do you have a copy of that, Wendy? -- it assesses details
14 of spectacle wearing and contact lens wearing, which we
15 thought was a major outcome variable. It addresses overall
16 satisfaction. If you'll let me just get a copy of that,
17 I'll tell you the other questions.

18 DR. HIGGINBOTHAM: Maybe I can ask my other
19 question since I have the floor now.

20 Dr. Macsai, did you finish your questions?

21 DR. MACSAI: Yes.

22 DR. McCULLEY: There was one that you asked
23 before that you didn't ask this time, and that was the
24 explanation of the changing N.

1 DR. MACSAI: Oh, yes. Well, I think I might
2 have figured it out since I asked it. I mean, is this
3 because you separated out only the patients with -7.0 and
4 1.0 diopter? But even if you did separate out just the
5 patients with -7.0 and 1.0 diopter, the N should either be
6 218 or 302. It shouldn't be both in these things you gave
7 us.

8 DR. THOMPSON: In the under 7.0 subgroup, we
9 looked only at patients that were under 7.0 diopters whose
10 best spectacle corrected acuity was 20/20 or better, and
11 who did not have monovision as an intended goal. So that
12 number would be lower than the total data set.

13 In addition, the reason that the N varies
14 between three, six, and 12 months is because the different
15 numbers of patients were available for follow-up at those
16 intervals.

17 DR. MACSAI: Excuse me, Dr. Thompson, but
18 unless you've mislabeled your slide, it appears that the N
19 is 302 at 12 months and 218 at six months.

20 DR. THOMPSON: Could you tell me which slide
21 you're referring to?

22 DR. MACSAI: 62 and 65. It seems those should
23 be the reverse. You have more patients followed up at 12
24 months than at six.

1 DR. THOMPSON: You're referring to the N of 218
2 at six?

3 DR. MACSAI: Yes.

4 DR. THOMPSON: And that's 218 at six.

5 DR. BULLIMORE: This is not the 65 that we have
6 on our handouts.

7 DR. MACSAI: No, my 65 is different.

8 DR. THOMPSON: Oh, I'm sorry. That's correct.
9 The handout you have has an error in it, and I apologize
10 for that. We actually detected that yesterday.

11 DR. MACSAI: Perhaps I should tell you the
12 title of the slides I'm referring to.

13 DR. THOMPSON: Okay.

14 DR. MACSAI: "Unaided Vision 20/40 or Better,
15 12-Month or Last Visit," N=302.

16 DR. THOMPSON: That's this one.

17 DR. MACSAI: Okay. And "Loss of Two Lines or
18 More of Best Spectacle Corrected Visual Acuity and Less
19 Than 20/40, Six Months" --

20 DR. THOMPSON: Oh, I think I understand why.

21 DR. MACSAI: Is that because you have last
22 visit of three months included, or what?

23 DR. THOMPSON: Yes. I should have labeled
24 those differently and clarified it for you. This is 12

1 month data for Summit and VISX, and this is our last visit
2 data in Group 1, and that's where we get our N of 302.

3 DR. MACSAI: Oh.

4 DR. THOMPSON: We have more patients here, and
5 that's why this was selected. So it's 12-month for Summit
6 and for VISX, and it's our last visit data.

7 DR. MACSAI: After enhancements?

8 DR. THOMPSON: Correct.

9 DR. BULLIMORE: Could you go forward two
10 slides? Thank you. So now you have on this slide 302 at
11 six months, and this is for your data you have 302. If you
12 were to go back five slides, you have 218 patients at six
13 months.

14 DR. MACSAI: Yes. I'm really confused.

15 MS. WONG: Mr. Chairman? I'm sorry to
16 interrupt. My name is Gwynne Wong. I'm with the FDA, and
17 I was the team leader for the Summit PMA. I would like to
18 point out that the data at one year for Summit would not be
19 considered statistically valid, and therefore I do not
20 believe comparison to the one-year data with 82 patients is
21 a valid comparison.

22 DR. McCULLEY: Thank you.

23 DR. THOMPSON: This is Dr. Thompson. We were
24 asked by the agency to make some comparison, and the

1 documents that we were provided were the PMA summary. So
2 that's the information that's summarized for you.

3 DR. MACSAI: But you haven't explained this
4 still. I'm sorry. Perhaps you could, because in some of
5 these six-month slides --

6 DR. CARR: I can answer that question. The
7 six-month slide you're looking at here with an N of 218 is
8 purely a six-month interval loss of best corrected acuity.
9 The other N's that you were looking at were last visit N's,
10 the 302, which is higher. So 218 in this slide refers to
11 the interval loss.

12 DR. MACSAI: Well, what about the percentage of
13 patients overcorrected by more than 1.0 diopter at six
14 months? That slide. Is that mislabeled? Right there.
15 Did you mean to have --

16 DR. CARR: You're correct, that is actually
17 mislabeled. The Emory data that are quoted there are last
18 visit.

19 DR. THOMPSON: So this is mislabeled. Instead
20 of it being six months, it should be last visit, correct?
21 Six months for Summit and for VISX, that's correct, and
22 that should be last visit for the Emory data.

23 DR. WARING: Dr. Macsai, please appreciate the
24 challenge that the agency gave us in the latter stages of

1 the process, to take the previous PMAs which had fixed
2 steps in them and did not necessarily correspond to our
3 fixed steps and try to do those comparisons. We realize we
4 did our subset, we made them as comparable as possible,
5 but, in fact, since the trials were carried out under
6 entirely different protocols, making them match accurately
7 will give some floating numbers because we were trying to
8 find our subset that was closest to what was already
9 reported.

10 DR. McCULLEY: What you're saying is the FDA
11 asked you to compare to the previous PMAs?

12 DR. WARING: That's correct.

13 DR. McCULLEY: Really? Geez.

14 DR. MACSAI: Well, I would also have to ask you
15 to have patience with those of us who've only had two
16 minutes to look at this complicated data.

17 DR. WARING: You did splendidly in two minutes.

18 DR. McCULLEY: Dr. Eydelman?

19 DR. EYDELMAN: I just want to clarify
20 something. First of all, no formal request has been made
21 of the sponsor to have any new data for the panel today.
22 We had a telephone conversation in which we were discussing
23 certain issues that might come up at the panel which might
24 be of importance for which we lack data as of today.

1 During that discussion, I brought up that the data in the
2 submission for patients with below 7.0 diopters was not
3 grouped and presented in a manner which would be easily
4 comparable to prior approvals or refractive guidance. To
5 that, the sponsor has undertaken this effort. However, as
6 I said once before, we have never requested that this was
7 performed or done.

8 DR. McCULLEY: Okay. I think there must be
9 some --

10 DR. MACSAI: Some communication --

11 DR. WARING: No, there's not. What Dr.
12 Eydelman said is completely accurate and completely
13 correct. We submitted our information as you have it on
14 your desk. The agency was very, shall I say, helpful in
15 giving us guidance for this presentation. They said one of
16 the things that might clarify what you're doing is to try
17 to make comparisons with previously reported groups under
18 7.0. That was not a formal request. It was a suggestion
19 for clarification, and that's why we present this
20 information. It is not in our formal submission, but you
21 do have it in front of you, and you did great in two
22 minutes.

23 DR. McCULLEY: I'm not going to touch that one.

24 (Laughter.)

1 DR. WARING: Dr. McCulley, may I respond to the
2 previous question about the questionnaire? I do have that
3 answer now.

4 DR. McCULLEY: Yes.

5 DR. WARING: The question asked, if I
6 understand it, was what are you asking in your
7 questionnaire, what information are you after? The
8 questionnaire consists of a total of 39 questions, many of
9 them extracted from and patterned after the PERK
10 questionnaire document, but much more concise. Questions 1
11 through 24 -- that is, a little more than half -- simply
12 address the glasses or contact lens wearing status: how
13 often for distance, how often for near, how much for right
14 eye, how much for left eye. We were trying very hard to
15 get information which is, more or less, not published at
16 all in the refractive surgery literature about this
17 important outcome variable for the patient, how often are
18 you out of your corrective lenses.

19 Questions 25 through 29 have to do with
20 subjective assessment of the simultaneous versus sequential
21 -- which way did you have it, which way would you like to
22 have it.

23 DR. MACSAI: Excuse me, Dr. Waring. We have
24 ~~this, in case the panel wants to look it up to make your~~

1 life a little easier.

2 DR. HIGGINBOTHAM: Where is it located?

3 DR. MACSAI: It's in Volume I of IV, the first
4 light blue one, on page 65. I'm sorry to interrupt you.

5 DR. WARING: I don't mind at all. If you want
6 me to stop, I will.

7 DR. HIGGINBOTHAM: Dr. Chair, just a couple of
8 more questions, because this will help me answer at least
9 my first question. This is Dr. Higginbotham. This will
10 help me answer one of the panel questions that we have, and
11 that's Number 7. Thank you for expanding on the patient
12 questionnaire issue. This will require I think Dr.
13 Eydelman to maybe come to the microphone just for
14 clarification.

15 It's my understanding that at 12 months, by FDA
16 definition of "follow-up", that there are only 55 percent
17 of the cohort available. Is that right, Dr. Eydelman? For
18 Group 1.

19 DR. EYDELMAN: We don't have necessarily formal
20 follow-up definition in the guidance. However, yes. Since
21 no other explanation was provided for the subjects, and we
22 know that there were no deaths occurring, I can't account
23 for them in any other fashion except to call them loss to
24 follow up.

1 DR. HIGGINBOTHAM: Okay. Dr. Waring, in your
2 elegant presentation, you alluded to the fact that there
3 was an extremely high level of patient satisfaction. Is
4 that right?

5 DR. WARING: Based on the answer to one of the
6 questions in the questionnaire on a small sample size at 12
7 months.

8 DR. HIGGINBOTHAM: Okay. My question then is,
9 is that the total 200-some-odd patients, 55 percent, or a
10 subset even of that population?

11 DR. WARING: A subset.

12 DR. McCULLEY: You reported 100-and-something
13 that had done the questionnaire.

14 DR. WARING: Yes. We had about 140 responses
15 maybe out of 200. Not all the patients would complete the
16 questionnaire.

17 DR. HIGGINBOTHAM: I see. So it's roughly
18 about 25 percent or so of the available patients --

19 DR. WARING: No. It's roughly about 75 percent
20 of the available patients.

21 DR. McCULLEY: It's 135 to 140 patients.

22 DR. WARING: It's about 135 out of the roughly
23 200 seen at 12 months.

24 DR. HIGGINBOTHAM: Dr. Eydelman, do you want to

1 expand? Because I have in my notes that 200-plus would be
2 available.

3 DR. EYDELMAN: I believe 205 eyes were examined
4 at 12 months. I think what Dr. Higginbotham is trying to
5 make the difference, if I understand, is how many eyes
6 should have been examined. In other words, how many were
7 available for exam at 12 months. Is that correct?

8 DR. HIGGINBOTHAM: Patients physically who
9 could have filled out the form, who did indeed fill out the
10 form. I'm just trying to get a sense of the denominator.

11 DR. McCULLEY: I think, just to clarify for a
12 moment, we had 205 patients or so examined at 12 months.
13 Correct? You have patient questionnaires that you
14 presented information on, on 135 to 140. I saw both those
15 numbers. So of the 205, only 135 or 140 responded. I
16 guess your question is, why isn't it 205?

17 DR. HIGGINBOTHAM: Exactly. Do we have any
18 information --

19 DR. ROSENTHAL: Excuse me. This is Dr.
20 Rosenthal. The issue is 205 were examined, 140 answered
21 the question. Now Dr. Eydelman will tell you how many
22 could have been examined.

23 DR. McCULLEY: That's yet another issue.

24 ~~DR. MACSAI: That's a separate issue.~~

1 DR. HIGGINBOTHAM: That's a separate issue.

2 DR. MACSAI: Why didn't 65 fill out the form?
3 That's the question.

4 DR. ROSENTHAL: I beg your pardon. I'm sorry.

5 DR. McCULLEY: This is not an accountability
6 issue. This is why did not all 205 fill out the
7 questionnaire? It's an easy question.

8 DR. RUIZ: They never do.

9 DR. HIGGINBOTHAM: Well, I guess my question
10 is, do you have a sense as to whether or not the remaining
11 available patients did not fill out the questionnaire
12 because of lack of satisfaction? I mean, this really does
13 pertain to the last question that the panel has in front of
14 us in terms of answering the FDA. Do you have an idea in
15 terms of why? Or is there a level of dissatisfaction, and
16 that may have contributed to their not filling out the
17 questionnaire?

18 DR. WARING: We have no data on that. They did
19 come back for the follow-up exam. I can give you my
20 subjective impression, that a lot of these people at 12
21 months come back only because we brow-beat them to come
22 back. They don't think they need to. They paid for the
23 exam, they're fed up with these tests, and they do it only
24 out of some sense of personal obligation to their doctor.

1 Then we give them a questionnaire that's supposed to take
2 an hour or an hour and a half of their time to fill out,
3 and it's like junk mail. They just say, "Dr. Waring, thank
4 you for this, but I don't have time to do it now." It's
5 not because they're dissatisfied or something
6 systematically. It's just that they feel they've done
7 their job.

8 Now, one reason, as Dr. Eydelman pointed out in
9 her fine review, that we don't consider patients lost to
10 follow-up by, shall we say, the conventional definition
11 because they weren't examined in that timeframe, is that
12 we're still going to send another questionnaire out to
13 these folks who haven't filled it out and we're going to
14 attempt, as we complete our 12-month follow-up, to be as
15 thorough as possible. So we haven't given up on these
16 people yet.

17 The succinct answer is no, we don't think
18 there's a systematic bias in non-responders.

19 DR. HIGGINBOTHAM: Was there an attempt to mail
20 questionnaires to those 45 percent of the available
21 patients at 12 months who --

22 DR. WARING: Yes.

23 DR. HIGGINBOTHAM: And you had no responses, no
24 sample from that population?

1 DR. WARING: I don't know the answer to that.
2 Those data are not tabulated, but I do know that we haven't
3 given up yet.

4 DR. THOMPSON: This is in progress.

5 DR. WARING: That is correct, and we indicated
6 that in our primary submission.

7 DR. HIGGINBOTHAM: My second question is just
8 really to help me understand your data. My impression is
9 that in Group 2, the outcomes are slightly better in terms
10 of the number of people that are not overcorrected because
11 you're doing more of the enhancements, et cetera. You have
12 three new surgeons --

13 DR. WARING: That is incorrect.

14 DR. HIGGINBOTHAM: That's not correct?

15 DR. WARING: Yes. We dropped out three
16 surgeons and added none.

17 DR. HIGGINBOTHAM: Oh, I see.

18 DR. MACSAI: Excuse me. I thought you did add
19 them. No, you didn't. So you started with 12 and you
20 ended with nine?

21 DR. WARING: We started with 14 --

22 DR. MACSAI: I mean 14, and ended with 11?

23 DR. WARING: Yes, and those 14 were dropped out
24 in process, not all at the credentialing level. Some of

1 them did a few cases and stopped, but we froze the
2 investigator entry at that initial time and we added no new
3 investigators.

4 DR. MACSAI: And the investigators for Group 2
5 are a subset of Group 1?

6 DR. WARING: Well, there are three less people
7 operating in Group 2 than there were in Group 1.

8 DR. McCULLEY: So there are 11 people. Thank
9 you for that clarification.

10 DR. MACSAI: Okay, now I understand.

11 DR. McCULLEY: Dr. Higginbotham?

12 DR. HIGGINBOTHAM: Just a very quick question.
13 So we have no idea in terms of the power of the new
14 nomogram in terms of improving the outcomes versus whether
15 or not a new surgeon may have the same difficulty in
16 learning this nomogram as well.

17 DR. WARING: Let me be real, real clear about
18 this. I'm going to try again. There is no difference in
19 the surgical technique between Group 1 and Group 2. The
20 only difference between Group 1 and Group 2 is laser
21 dosing, how many shots are given for a given refractive
22 baseline error. All operational issues in Group 2 are
23 identical to the operational issues in Group 1.

24 DR. McCULLEY: And there were no new surgeons.

1 DR. WARING: And there were no new surgeons in
2 Group 2 compared to Group 1.

3 DR. HIGGINBOTHAM: Including the number of
4 enhancements. Is that right?

5 DR. WARING: That's correct.

6 DR. HIGGINBOTHAM: Well, I appreciate you
7 making that very clear, Dr. Waring.

8 DR. FERRIS: But it seems to me we need to make
9 clear that surgical experience, by definition, is different
10 in Group 1 and Group 2. Those 11 surgeons are more
11 experienced at the time of Group 2 than they were at the
12 time of Group 1.

13 DR. WARING: That's completely correct.

14 DR. FERRIS: So there is some inherent problem
15 of confounding. If you were trying to look at the nomogram
16 alone, it's somewhat confounded by surgical experience.
17 Perhaps you could deal with that by taking -- apparently
18 you have two or three or four, I don't know how many
19 surgeons who were pretty experienced before they started
20 Group 1, and you might look at those within that subset, if
21 you were trying to look just at the nomogram, to try to
22 factor out surgical experience.

23 DR. WARING: That's a very good point and I
24 fully agree with that, and there is that time difference,

1 but no structural differences. I just want the panel to
2 understand that we didn't change the protocol except for
3 the dosing between Group 1 and Group 2.

4 DR. McCULLEY: And you didn't change your
5 investigators.

6 DR. WARING: And we didn't change the
7 investigators, but experience increased.

8 DR. MACSAI: Excuse me. Who is Steven
9 Hamilton?

10 DR. WARING: Steven Hamilton is an
11 ophthalmologist in Atlanta.

12 DR. MACSAI: Well, he's listed under Group 2
13 but not Group 1.

14 DR. WARING: When did Steve Hamilton join?

15 DR. McCULLEY: George, you really got to pay
16 attention to every little detail.

17 (Laughter.)

18 DR. WARING: That's okay. That's why we have a
19 panel to help us.

20 I'm wrong, Dr. Macsai, and you're correct. We
21 added one investigator, Dr. Hamilton, who is a partner of
22 one of the senior investigators. You're correct, I made an
23 error.

24 DR. McCULLEY: Can we ask if there were any

1 particular factors that could be related to his joining or
2 any insights you would have gained from him joining at the
3 time that he joined that would shed light on our
4 deliberations now?

5 DR. WARING: No. Dr. Hamilton went through the
6 formal credentialing process that I outlined for you
7 before.

8 DR. McCULLEY: There was nothing in his entry
9 and his performance that was different.

10 DR. WARING: That's right. He did not have any
11 more complications than anybody else.

12 DR. HIGGINBOTHAM: That was my follow-up
13 question, Dr. Chair, that I was not able to ask before.
14 Thank you. This is Dr. Higginbotham.

15 DR. MACSAI: Dr. Waring, this is Dr. Macsai
16 annoying you yet again.

17 (Laughter.)

18 DR. MACSAI: Now the question is, this is why
19 I'm interested in the intraoperative complications in Group
20 2, because of this addition of Steven Hamilton. If indeed
21 they are volume-related complications, they might go up,
22 and I was curious to see if you've looked at that.

23 DR. WARING: The answer is no. Your question
24 is an excellent question, and the answer is no, we don't

1 have those data for Group 2.

2 DR. McCULLEY: Thank you.

3 Dr. Higginbotham, did you have any additional
4 questions?

5 DR. HIGGINBOTHAM: Not at this time, Dr. Chair.
6 Thank you.

7 DR. McCULLEY: "Hey you" would be better than
8 "Dr. Chair."

9 (Laughter.)

10 DR. SUGAR: Just one question for my review.
11 Did you get indices of irregularity on your topography, and
12 do you have any comparisons between groups or between
13 degrees of refraction correction?

14 DR. WARING: We did not do any formal analyses
15 of keratography, and we explained the reasons for that in
16 our primary submission. We did, then, in response to the
17 agency's request, submit the keratographs on all eyes that
18 lost two or more lines of spectacle corrected visual
19 acuity, and we characterized in a qualitative way the
20 patterns, but we did not do quantitative indices analysis
21 on those eyes.

22 DR. McCULLEY: Did it give you any insights as
23 to why the patients lost two lines?

24 DR. WARING: Yes. What we observed and what we

1 reported in the document was that it was a highly variable
2 response. I don't know who the commentator was, but one of
3 the commentators observed this, that in these eyes that
4 lost two or more lines, the predominant pattern was a round
5 central circular flat zone, which we would associate with a
6 good outcome. But we don't have any control data for that
7 in eyes that did not, and we don't have any quantitative
8 data.

9 DR. McCULLEY: Thank you.

10 Dr. Ruiz?

11 DR. RUIZ: Let me ask a few simple questions.
12 How do these folks tolerate contact lenses after surgery?

13 DR. WARING: To the best of my knowledge --
14 I'll ask my colleagues -- we have fit nobody with contact
15 lenses afterwards, except for one patient that I can recall
16 who has some irregular astigmatism, and that fitting was
17 done at the Emory Eye Center, and that person is a
18 successful contact lens wearer now.

19 DR. RUIZ: Would you anticipate any problems
20 with the flap and so on?

21 DR. WARING: To the best of my knowledge, no,
22 and I say this partly on our experience, which is
23 minuscule, for fitting contacts, but remembering that

24 ~~keratomileusis as a surgical procedure has been done for 30~~

1 years, a number of patients with keratomileusis ended up
2 with irregular astigmatism, and a number of patients with
3 ALK ended up with irregular astigmatism in the cohort, and
4 we've had a number of those fit with contact lenses without
5 the flap coming loose.

6 DR. RUIZ: Thank you. Maybe you presented
7 this, but what are the percentages of enhancement? In
8 other words, one enhancement -- what percentage of cases
9 had one enhancement?

10 DR. WARING: Dr. Ruiz, I can tell you generally
11 that it's 30 percent, and if we can find the slide, I can
12 give you exact --

13 DR. RUIZ: It might have been in the 20s, and
14 you quote 30 percent when you're talking to the patients
15 preop.

16 DR. WARING: Yes.

17 DR. RUIZ: I'd like to know what the percentage
18 of secondary enhancements were, and how many of them needed
19 a third, if you have that data.

20 DR. McCULLEY: Dr. Eydelman?

21 DR. EYDELMAN: I have quoted these numbers for
22 subjects with LASIK only as a primary procedure in my
23 Amendment 4 and 5 review on page 8. Basically for Group 1,
24 ~~44 percent of the eyes underwent any enhancement procedure.~~

1 That's LASIK only or LASIK plus ARC or ARC-T only. In
2 Group 2, 16 percent had an enhancement so far.

3 DR. RUIZ: How many had a second enhancement?

4 DR. EYDELMAN: In Group 1, 5 percent had two
5 enhancements, and 0.8 percent had three enhancements. This
6 is counting all types of enhancements.

7 DR. RUIZ: Thank you. That answers it for me.
8 Thank you very much.

9 What is the time interval that you wait before
10 you enhance?

11 DR. WARING: The time interval prescribed in
12 the protocol is three months, and we wait three months.

13 DR. RUIZ: And when you lift the flap, you do
14 that with a Sinsky hook or a fine spatula?

15 DR. WARING: That's correct.

16 DR. RUIZ: And so you disrupt the epithelium.
17 You don't incise it, you actually just part it. You must
18 create in quite a few of these patients an epithelial
19 defect. The reason I bring this up is because in the
20 surgical technique that I use for cataract, using a diamond
21 knife, you will notice that sometimes that epithelium won't
22 cut. It just kind of peels off in front of the knife. You
23 must have a lot of epithelial defects when you enhance.

24 DR. WARING: This is Dr. Waring, and you are

1 correct. If you look at primary procedures -- this is not
2 our work, it's work that came out of Israel this past year
3 -- 10 percent of eyes have "loose" or easily disrupted
4 epithelium. In my experience, subjectively, this is right,
5 but we did not quantify it in this trial.

6 The roughness of the epithelial edge of the
7 flap is greater after lifting it for an enhancement than it
8 is after the primary cut, and I would say this is true in
9 almost 100 percent. Not quite -- sometimes the epithelium
10 stays put. But in the vast majority of cases, there's one
11 clock hour at least where there's an irregular epithelium
12 that would constitute an epithelial defect close to the
13 edge, but not enough of a defect to create edema in the
14 flap, and that seems to be the differentiating factor in
15 terms of epithelial ingrowth, for example.

16 Let me just say one other thing that we always
17 tell patients after an enhancement, that they will have
18 more discomfort after the enhancement than after the
19 primary procedure for the reason you point out, that the
20 epithelial edge is rougher than it is after the clean cut
21 of the microkeratome.

22 DR. RUIZ: Thank you. One other question. The
23 area of the laser -- let's talk in diameters. The diameter
24 of the ablation zone vis a vis the diameter of the lamellar

1 bed.

2 DR. WARING: This is George Waring. The
3 diameter of the lamellar bed is 8.5 millimeters, on
4 average. It varies some depending on the corneal
5 curvature. The diameter of the ablation in single zone is
6 6.0 millimeters, and in multizone is 6.5 millimeters. We
7 have no overlap, then, between the edge of the cut and the
8 edge of the ablation, unless the hinge is a little bit
9 towards the center, in which case the ablation can overlap
10 the hinge a little bit, and in that case we place a
11 blocker, a cellulose sponge or something on the hinge so we
12 don't ablate the hinge.

13 DR. RUIZ: Thank you.

14 DR. McCULLEY: Are there any other questions
15 for the sponsors?

16 DR. BULLIMORE: Yes. This is Dr. Bullimore.
17 I'll save my comments for later, but I have a couple of
18 questions relating to enhancement procedures. This seems
19 to be a paradox in the data, that being that for the Group
20 1 patients, the enhancement rate was about 41 percent, and
21 for the Group 2 patients it's 16 percent. Given what you
22 did to the algorithm or nomogram, whatever you want to call
23 it, to shift it in the undercorrected direction, one would
24 anticipate that the effect of that would be an increased

1 number of enhancements in the Group 2 patients. Can you
2 explain what I see as a paradox?

3 DR. McCULLEY: It's not a paradox. You can
4 answer that very quickly.

5 DR. THOMPSON: This is Dr. Thompson. There are
6 two answers. One is the Group 2 patients haven't been
7 followed as long as the Group 1 patients, so the
8 enhancement rate is going to go up, Dr. Bullimore. The
9 second reason that the panel may not be aware of is that as
10 we progressed in Group 1, it became evident to the surgeons
11 that we were overcorrecting patients. In order to be
12 conservative, we intentionally began to back off of the
13 treatment.

14 DR. BULLIMORE: So there was a kind of Group 1
15 and a half patients.

16 DR. THOMPSON: There you go.

17 DR. BULLIMORE: A question relating to
18 sequential versus simultaneous. I respect my colleague's
19 opinion about the practice of medicine. Do you use two
20 keratomes or one keratome for simultaneous?

21 DR. THOMPSON: This is Dr. Thompson. We use
22 one.

23 DR. BULLIMORE: You use one. I'm sort of naive
24 to this. Is there any sort of cleaning or scrubbing that

1 needs to be done between the procedures, or you just strap
2 it off one and onto the other?

3 DR. THOMPSON: That's correct, the latter. We
4 don't do anything to the microkeratome in-between eyes.

5 DR. BULLIMORE: Okay. I'm saving my broader
6 questions to the end, so bear with me here. You don't want
7 to answer questions on multifocal IOLs, obviously.

8 Intuitively, given what's been done in the low
9 myopic patients -- i.e., 7.0 diopters and below --
10 intuitively I would have expected you'd get better
11 predictability with LASIK than straight surface PRK.
12 That's not the case. Have you any explanations for that?
13 I don't need the slide, just tell me what you think.

14 DR. THOMPSON: I'm not sure that I agree with
15 your premise. I think our analysis showed that the
16 standard deviation in our group was a little bit better
17 than that for PRK, if I recall.

18 DR. BULLIMORE: So you're saying it's not --

19 DR. THOMPSON: It's not a huge number. I think
20 the standard deviation at 12 months was slightly lower for
21 our LASIK subset.

22 DR. BULLIMORE: Was that based on one or two or
23 three procedures? I mean, is that primary procedure only
24 or with enhancement?

1 DR. THOMPSON: This would include enhancements.
2 So to get a true head-to-head comparison, we would have to
3 recompute this with one procedure only.

4 DR. BULLIMORE: I think Dr. Eydelman may have
5 done that already and I won't dwell on that. One other
6 question relates to the interim visual acuity of your
7 subjects. I noticed on the data that you presented -- this
8 was Dr. Waring's graphs that he started showing us early on
9 in the proceedings -- the slide I have numbered at 30 says
10 that you have, I think, 11 patients with 2,400 or worse
11 best corrected acuity. Is that correct or is that another
12 typo?

13 DR. MACSAI: That's what it says on the slide.

14 DR. WARING: Tell me the slide number again,
15 Dr. Bullimore?

16 DR. BULLIMORE: On the handout you gave us,
17 it's slide 30. So you've got 11 patients entering your
18 trial with best spectacle corrected visual acuity at
19 enrollment of 2,400. Is that correct?

20 DR. WARING: That's correct. These are eyes,
21 not patients, but the idea is correct.

22 DR. BULLIMORE: But then when we look to
23 follow-up, the worst visual acuity you presented to us is
24 20/80. What happened?

1 DR. WARING: Most of these patients with high
2 myopia wear contact lenses. All of these measurements are
3 taken with spectacles, which, as you well know, don't give
4 as good vision as contact lenses, and then we --

5 DR. BULLIMORE: I don't know that, but I'll
6 accept your explanation for the moment.

7 DR. WARING: And then we think that the
8 magnification factor that we mentioned before, that is
9 getting rid of the myopia, improves spectacle corrected
10 visual function. So you take a lens that's 11.0 diopters
11 or 15.0 diopters thick and reduce that to a lens that's 1.0
12 diopter thick, the patient can then see better, has
13 improved spectacle corrected visual acuity over what they
14 did at baseline.

15 DR. BULLIMORE: So you're suggesting to me that
16 you got a factor of 3 improvement in the limited resolution
17 of an eye that you attribute to image magnification?

18 DR. WARING: Yes.

19 DR. BULLIMORE: Excuse me, but I don't buy it.
20 Even in a 15.0 diopter myope, one would only expect a 1-
21 or, for an extreme distance, a 2-line acuity improvement,
22 and we got this. I don't want to dwell on it, but this
23 seems to be an inconsistency in your data that I find just
24 a little difficult to explain. I really don't accept your

1 explanation is what I'm saying. That's all I have to say
2 at the moment.

3 DR. McCULLEY: Are there any other -- you're
4 pressing your quota.

5 (Laughter.)

6 DR. MACSAI: I am pressing my quota because I
7 found different things in the data. My understanding is,
8 in Group 1 alone, there were four patients fit with soft
9 contact lenses, full-time wear, and one in rigid gas
10 permeables.

11 DR. McCULLEY: Postop.

12 DR. MACSAI: Postop.

13 DR. WARING: I'm going by my memory and I don't
14 know. It's a very small number. The answer to Dr. Ruiz'
15 question is yes, you can fit contact lenses afterwards, and
16 the answer to you is no, I don't remember how many eyes we
17 did do that on. But I would stand by the data as
18 published, not my memory.

19 DR. MACSAI: Okay, because in here it's
20 different.

21 DR. WARING: Yes. The problem with that is
22 that my memory is skewed by my patients and not the
23 hundreds done by other surgeons.

24 DR. McCULLEY: Just a point of clarification.

1 You are responsible for the data, you guys.

2 DR. WARING: That's correct. That's why I
3 shouldn't go by my memory.

4 DR. McCULLEY: Right.

5 Dr. Soni?

6 DR. SONI: Dr. Waring, you presented data to
7 suggest that 92 percent of the patients either wore their
8 glasses part-time or never wore them. Can you give me data
9 on how many never wore them?

10 DR. WARING: Yes, just give me a second. You
11 see I'm not going by my memory. This is based on the
12 limited sampling of 152 patients for this particular
13 question. Fifty-nine percent wear no glasses at all for
14 distance or near. In terms of distance wear, let me give
15 you the analysis. Among the 31 percent of the 143
16 respondents that wear lenses at all, 15 percent of the
17 total use them for reading only, 13 percent of the total
18 use them for distance only, and 13 percent use them for
19 both purposes. Ninety-two percent of patients do not wear
20 corrective eyewear full time. In other words, 8 percent
21 wear corrective eyewear full time.

22 DR. McCULLEY: Does that answer your question?

23 DR. SONI: Yes.

24 DR. McCULLEY: ~~Are there any other questions~~

1 for the sponsors? Dr. Ferris, do you have any additional
2 questions?

3 DR. FERRIS: I have a bunch of comments which
4 I'll save because it's lunchtime, but I do have a question
5 I'd like to ask, and that is --

6 DR. McCULLEY: I think for now we want to be
7 sure, because once we break for lunch, the sponsors will be
8 excused from the table. So any questions for the sponsors
9 that anyone wants to ask, now is the time to ask them.

10 DR. FERRIS: If I understood what you said,
11 your questionnaire may be somewhat onerous if it takes an
12 hour to an hour and a half to fill out. I was wondering if
13 you had given any thought to a shorter questionnaire that
14 you might get virtually, at least hopefully, 90 to 100
15 percent response to, because this issue of loss to follow-
16 up is a critical one and we don't know what's happened to
17 people that you don't have any information on. Anything
18 you could do to improve that would be helpful. If you
19 called me up and told me you had an hour and a half worth
20 of questions to ask me, I can guess what I'd say.

21 (Laughter.)

22 DR. McCULLEY: We're going to have a discussion
23 period. The issue now on the floor are questions for the
24 sponsor. Does anyone else have any other questions?

1 DR. WARING: May I respond to that question
2 about the questionnaire?

3 DR. McCULLEY: It was a statement, but okay.

4 DR. FERRIS: No, no, it was a question.

5 DR. WARING: Dr. Ferris, this is Dr. Waring. I
6 agree with exactly what you said. Our design of the
7 questionnaire took the PERK questionnaire, which took two
8 hours to fill out, and reduced it to approximately 50
9 questions, which we thought was roughly a minute per
10 question and could be filled out. If we reduce it down
11 further and make it more succinct, then we run afoul of the
12 questions we've already been asked where we have no
13 information about glare, no information about halos.
14 That's already been cut out of the previous questionnaire.
15 So it's a difficult balance how much do you ask, and if
16 it's too succinct, you don't get the answer.

17 Let me reinforce your point that we don't like
18 the loss to follow-up either, and that's why we don't call
19 these patients who we still know where they are lost to
20 follow-up because we're still in pursuit of them to fill
21 this questionnaire out.

22 DR. McCULLEY: Does that effectively deal with
23 your question?

24 DR. FERRIS: Yes.

1 DR. McCULLEY: Okay.

2 Dr. Bullimore?

3 DR. BULLIMORE: A couple of questions. You
4 related there was the unfortunate incident of the patient
5 who had a previous penetrating keratoplasty. Were there
6 other patients enrolled in this study who had a prior
7 penetrating keratoplasty?

8 DR. WARING: You can bet I'm not going to trust
9 my memory.

10 DR. BULLIMORE: I see Dr. Eydelman -- I'll take
11 an answer from wherever it comes.

12 DR. MACSAI: Yes, there were.

13 DR. BULLIMORE: How many, or approximately?
14 Was it 5, 10, 20, 50, 100?

15 DR. MACSAI: It was about -- it was a small
16 number.

17 DR. BULLIMORE: I'll look it up myself.

18 One bit of data that we haven't addressed and I
19 know we'll have to address later because it's on the list
20 of questions given to the panel by the FDA is the issue of
21 refractive stability. Much like your contrast sensitivity
22 data was a little more wobbly than one might like, this
23 seems to be. Feel free to put up a slide if you want to.
24 I'd be happy to look at it again. I think the issue raised

1 by Dr. Eydelman is that it's one thing to say that the mean
2 refractive error is constant within the postoperative
3 period, but does that mean being close to zero is just a
4 function of some random but large variation in the
5 refractive error of the patients? Then that is some cause
6 for concern.

7 It was actually the bar chart I wanted to look
8 at. Thank you. In that three- to six-month period where
9 you've got 490 patients, having 10 percent of your patients
10 increasing by a diopter and 7 percent decreasing by a
11 diopter, that's a substantial variability. Again, there
12 are two possibilities I can come up with. One is your
13 technicians or whoever else is doing the refraction is more
14 variable than people that have published their data in the
15 literature, because certainly one would anticipate on a
16 stable group of patients that in excess of 95 percent would
17 be within a diopter on successive refractions, or we've got
18 a situation where we've got an unstable eye. We have the
19 refractive error changing.

20 Now, I don't know the answer, but the burden of
21 proof, I guess in any PMA, falls upon the sponsor to
22 differentiate between those two possibilities. So I'd like
23 to hear your thoughts as to what the answer or your
24 impression is.

1 DR. WARING: This is Dr. Waring. I agree with
2 Dr. Bullimore that average values don't count when you can
3 go in two directions. They do give an indication of
4 overall population trends. For example, if we looked at
5 radial keratotomy, we would find a trend in the hyperopic
6 direction. So they help that, but they don't help us in
7 ferreting out the stability between intervals.

8 If we go to the next slide, your observations
9 are completely accurate that we have patients going in the
10 hyperopic and the myopic direction, and it's on the order
11 of 10 to 20 percent at the intervals during the first year
12 of follow-up, and this represents instability because we
13 have no way to determine whether it's variability in
14 measurement or variability in the eye. So we have to
15 assume, I think, that it's variability in the eye.

16 We were surprised to find this much
17 variability, and we were more surprised to find that it
18 went in two directions. That is, we can't counsel patients
19 or ourselves that they're more likely to move in the
20 hyperopic or in the myopic direction. But it does say that
21 there is this amount of variability in the first year after
22 LASIK.

23 DR. BULLIMORE: Thank you for reminding me
24 about the PERK study. I'll follow up on two issues related

1 to that. The first is, I guess, one of the major findings
2 of the PERK study was this persistent diurnal change in
3 refractive error. One explanation for this could be that
4 patients are examined at different times of the day on
5 different visits. Would you entertain that possibility,
6 that this is a manifestation of a diurnal change?

7 DR. WARING: Yes, I would. Some patients say
8 they see differently at different times of the day, and we
9 did no formal trials measuring the same patients in the
10 morning and the evening, as we did in PERK.

11 DR. BULLIMORE: The other is if you go back to
12 the previous line graph, I will accept that given the data
13 presented in these 200 patients over a 12-month follow-up,
14 there doesn't seem to be any trend. Casting my mind back
15 to the PERK data, and I will stand corrected if I
16 misrepresent this, it really took the 10-year follow-up to
17 demonstrate the persistent hyperopic shift that we observed
18 with RK. So that flat line notwithstanding, there is a
19 leap in faith in terms of long-term stability of refraction
20 in this and, indeed, any other refractive procedure. Would
21 you agree?

22 DR. WARING: No, I would not agree, because the
23 hyperopic shift in PERK was seen within the first year and
24 was well documented by the second year. So it didn't take

1 10 years to document it, it only took 10 years to quantify
2 how long does it last and how bad is it. I agree with your
3 premise that we do not know with certainty that LASIK is
4 stable after one year. We do not have those data in this
5 trial, and so we do not know. There is no trend line.

6 I will say again what I said before, that we've
7 been doing keratomileusis as a community for 30 years, and
8 although communities can have blinders on, if there were a
9 trend over, let's say, a decade towards steepening of the
10 cornea or further flattening of the cornea, you might think
11 this would show up in that time.

12 DR. BULLIMORE: Yes, but as you characterized
13 it yourself, this is not a community that's highly
14 motivated to publish their findings.

15 DR. WARING: That's correct.

16 DR. BULLIMORE: I frequently have students come
17 to me and say, "Can you give me some references for ALK?" a
18 procedure which has been around for a while, and I say,
19 well, there are one or two papers published in journals,
20 but there's really not the substance that you see in other
21 areas of ophthalmology and visual science.

22 DR. WARING: So our conclusion is that we only
23 know the data that we have within this first year.

24 DR. McCULLEY: Dr. Higginbotham?

1 DR. HIGGINBOTHAM: I think I'll ask my three
2 questions so I can get them asked, and then you can take
3 the floor.

4 My first question relates to your postoperative
5 use of steroids. Is there any prolonged use of steroids
6 postoperatively? As a glaucoma specialist, I would be
7 concerned, if that is the case, if you have looked at any
8 increase in intraocular pressure.

9 The second relates to Dr. Ferris' question,
10 which was a follow-up to mine regarding the questionnaire
11 and whether or not you looked at things like the NEI
12 quality of life questionnaire, which is much, much, much
13 shorter than what you have, and the VF14 as considerations
14 for assessing these patients' satisfaction with your
15 procedure.

16 Third, given the demographics of Atlanta, why
17 do you have such a lack of diversity in your cohort?

18 DR. WARING: I can answer those questions in
19 turn. Steroids are given in the form of a steroid-
20 antibiotic combination for five to seven days after surgery
21 and then stopped, and there is no prolonged use. We
22 measure intraocular pressure at every visit. And I don't
23 remember -- did we put the intraocular pressure
24 ~~measurements in the database that we turned in? Is that~~

1 correct? Yes. So those data have been submitted as part
2 of our core submission, but we did not identify a trend
3 toward elevated pressure because the steroids were short.

4 The second question regards the questionnaire.
5 The VF14 is an inappropriate questionnaire for refractive
6 surgery because it doesn't address lens-wearing use, and
7 this is a primary outcome variable that we think is
8 exceedingly important to assess and to assess carefully.
9 That's why we gave 20 questions to it in this
10 questionnaire, because those data just aren't available in
11 the community, and that's the patient's major concern. If
12 you add those questions on to the VF14, you now have
13 expanded your questionnaire to one that's a bit longer. We
14 would be very happy for consultation from anyone that is
15 expert in this area to help us develop a better
16 questionnaire. We do not think ours is a final instrument
17 that would be useful.

18 Your third question was racial mix and
19 diversity of our group. There are two reasons for that.
20 One is that our clinic is located in north Atlanta, which
21 is predominantly a white population. Although 70 percent
22 of Atlanta is black, with also a high Hispanic population,
23 the geographic distribution of race in Atlanta is
24 patterned, and we work in the predominantly white

1 community.

2 The second reason is that the expense of the
3 surgery, at \$5,000 an eye, is a --

4 DR. McCULLEY: An eye?

5 DR. WARING: Excuse me. I'm sorry -- \$5,000 a
6 patient, \$2,400 an eye, is a deterrent to people that don't
7 have enough money. And the third has to do with the
8 incidence of myopia, which I believe may be higher in the
9 white population than the black, but I don't think that's
10 the major reason for the white skew in our group.

11 DR. HIGGINBOTHAM: I believe there is a very
12 strong upper-middle-class population of African Americans
13 in Atlanta. Thank you.

14 DR. WARING: But in terms of the geography of
15 the distribution -- there's no question, the mayor of
16 Atlanta is black, the police chief is black. I suppose
17 it's fair to say that both those people have had LASIK in
18 our center. One of the major newscasters in Atlanta is
19 black and she has had that. So we certainly agree with
20 that.

21 DR. McCULLEY: Dr. Ferris, you had a question
22 about the questionnaire again? Let's finish that off.

23 DR. FERRIS: Just as a point of information,
24 the Eye Institute is currently working with some others to

1 try to develop a myopia-directed visual functioning
2 questionnaire to look at this issue because at least we
3 recognize that, as you point out, the current NEI, VFQ, or
4 the VF14, none of them is very well suited to answering the
5 questions related to problems of myopia. So that's in
6 development. That doesn't necessarily help you, but that's
7 a point of information you might be interested in.

8 DR. McCULLEY: Dr. Macsai?

9 DR. MACSAI: I have a very simple question.
10 What is, at the 12-month point, for Group 1 that's reached
11 12 month, what's your actual loss to follow-up rate, in
12 your definition? How many people have reached 12 months
13 that you haven't examined?

14 DR. WARING: We have reported that in one of
15 our amendments. That is, we have given the actual names of
16 the patients who we no longer can contact. Let me see if I
17 can get that number for you so you know how many we
18 consider to be permanently lost to follow-up because we
19 can't find them anymore.

20 DR. McCULLEY: Your definition of "lost to
21 follow-up" is that you don't know where they are.

22 DR. MACSAI: For the 12-month visit, that's
23 what I want to know, by your definition.

24 DR. McCULLEY: But you need to know what his

1 definition is.

2 DR. ROSENTHAL: Excuse me. I think the issue
3 is accountability and let's forget about loss to follow-up.
4 It's accountability.

5 DR. MACSAI: Okay.

6 DR. ROSENTHAL: Then it puts us on the same --
7 he's using a different definition than you and I might use,
8 but we're talking about accountability issues.

9 DR. MACSAI: Right.

10 DR. McCULLEY: By the FDA's definition, the
11 accountability at 12 months was roughly between 50 and 60
12 percent.

13 DR. ROSENTHAL: It was 55 percent at 12 months
14 for Group 1.

15 DR. McCULLEY: I think that that's really the
16 issue here.

17 DR. MACSAI: That means 55 percent of the
18 people that have reached 12-month exam. That's what I was
19 trying to clarify.

20 DR. McCULLEY: Yes. They're accounted for in
21 terms of exams.

22 DR. ROSENTHAL: That's correct.

23 DR. MACSAI: Okay. I'm done.

24 DR. McCULLEY: Dr. Soni?

1 DR. SONI: Talking about stability of
2 refraction, you and Mark were discussing that point earlier
3 on, and you both agreed that 12 months may not be adequate
4 time to be able to predict what the stability is going to
5 be. Are you following these patients beyond 12 months? I
6 know that addresses the accountability too, but to look at
7 specifically refractive stability, are you going to follow
8 these patients beyond 12 months?

9 DR. WARING: We're not following these patients
10 beyond 12 months. The initial IDE specified a 12-month
11 follow-up. We don't have the resources to follow them more
12 than 12 months, and the overall stability we think is
13 acceptable at a clinical level to allow us to deal with
14 that, even though I agree with Dr. Bullimore that the
15 actual stability beyond 12 months is simply unknown to us
16 because we're not following those patients.

17 DR. McCULLEY: Are there any other questions
18 for the sponsor?

19 DR. BULLIMORE: Yes. I'd just like some
20 clarification, and this may require some input from both
21 FDA and the sponsor. This concerns the certification,
22 training, accreditation of surgeons. I want to be sure
23 before we excuse the sponsor and deprive them of any
24 ~~further comment what we would be getting into and requiring~~

1 certification. Could we require it of the laser company?
2 Could we require it of Chiron or any other maker of a
3 microkeratome? Or is that purely the domain of the
4 sponsor?

5 DR. McCULLEY: As a corneal surgeon, I'm
6 certain that there are requirements that will be met that
7 do relate to the laser, do relate to whatever microkeratome
8 is being used, and they have specifics that they said for
9 the Emory LASIK System would have to be met that they
10 enumerated at length. As a surgeon, I don't really feel
11 like I need to hear any more about that.

12 DR. BULLIMORE: Well, as a panel member, I'd
13 like to hear from both the --

14 DR. McCULLEY: Well, to use the laser, one has
15 to be certified. To use the microkeratome, one has to be
16 certified as the existing microkeratome that was used.
17 That is required by each entity separately.

18 DR. BULLIMORE: There were questions raised
19 earlier by two reviewers about the practice of medicine. I
20 want to know whether by approving this PMA, the impact that
21 would have on the practice of medicine. For example, let
22 me give you an extreme example. Let's suppose Dr. Waring
23 and his colleagues -- I don't expect them to do this,
24 ~~knowing them~~ ~~said, okay, we've got the PMA approved, but~~

1 we're not going to train anyone. If people want this
2 procedure, they have to come -- is that their prerogative?

3 DR. McCULLEY: I would like the FDA to respond
4 to that. I think we're getting into issues that maybe
5 aren't --

6 DR. BULLIMORE: I agree, but I wanted to raise
7 them while the sponsor still had the ability to have input
8 and before they were sort of dismissed from further
9 discussion.

10 DR. ROSENTHAL: I apologize, Dr. Bullimore. I
11 did not hear what the issue was. I had people talking to
12 me in both ears. I'm sorry. They were hearing, but I
13 wasn't.

14 DR. BULLIMORE: I'll repeat it briefly. Who is
15 going to be responsible or able to handle certification for
16 doing the procedure that we are being asked to vote upon
17 this afternoon? Does that responsibility fall solely with
18 the sponsor? Does it fall with anybody that makes a
19 microkeratome? Anybody who makes a laser? What are the
20 restrictions? Can they take their ball and go home?

21 DR. McCULLEY: It's technology transfer issues,
22 really.

23 DR. ROSENTHAL: My understanding is that we can
24 require the sponsor to provide a training program for

1 individuals who wish to use the sponsor's device.

2 DR. BULLIMORE: So the sponsor's device in this
3 circumstance --

4 DR. ROSENTHAL: Is all four things as a
5 package.

6 DR. BULLIMORE: So if somebody wanted to use a
7 different algorithm but nonetheless use the Chiron
8 microkeratome --

9 DR. ROSENTHAL: Then it's the practice of
10 medicine that has been well set out by the Office in the
11 October letter to all ophthalmologists.

12 DR. BULLIMORE: So why doesn't that constitute
13 off-label use of the laser?

14 DR. ROSENTHAL: Sorry?

15 DR. BULLIMORE: Why doesn't that constitute
16 off-label use?

17 DR. ROSENTHAL: That does constitute off-label
18 use. What wouldn't constitute off-label use is using the
19 device which has been put together by this sponsor.

20 DR. BULLIMORE: And using the sponsor's
21 nomogram?

22 DR. ROSENTHAL: Algorithm and nomogram.

23 DR. BULLIMORE: And being trained and
24 certified?

1 DR. ROSENTHAL: And being trained and
2 certified.

3 DR. BULLIMORE: Thank you.

4 DR. MACSAI: I think what Dr. Bullimore is
5 getting at is that Emory doesn't intend for everyone to
6 come to Emory to use their laser, that this is a device
7 that they're going to train --

8 DR. McCULLEY: Point of order, Dr. Rosenthal.

9 DR. ROSENTHAL: This is not an issue which is
10 to be discussed here --

11 DR. MACSAI: Oh, sorry.

12 DR. ROSENTHAL: -- about how the sponsor wishes
13 to market their device. That is their issue, which they
14 will decide in the future. Sorry, it's not for the panel's
15 discussion.

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

18 (No response.)

19 DR. McCULLEY: I have one. Have you done any
20 corneal thickness measurements? There has been, over time,
21 in our community of keratomileusis, et cetera, the
22 recognition that a certain amount of posterior corneal
23 stroma must be left behind in order to ensure corneal
24 stability over time. Have you assessed that safety issue

1 with your device?

2 DR. WARING: We've done no corneal thickness
3 measurements over time. We have left at least 280 microns
4 based on the calculations that were presented by --

5 DR. McCULLEY: No. The calculations that were
6 presented was the depth to which it went, George.

7 DR. WARING: Well, assuming a 550-micron-thick
8 cornea in the center, then we leave 280. If there are
9 corneas that are thinner, we don't know and we have not
10 done corneal thickness measurements over time.

11 DR. McCULLEY: Okay. I would think you would
12 agree that you can't assume all corneas are 550 microns,
13 and you would agree that there is an issue about amount of
14 posterior corneal stroma being left behind to ensure
15 stability over time.

16 DR. WARING: Yes, I agree that those are
17 issues.

18 DR. McCULLEY: That you didn't assess in this
19 application.

20 DR. WARING: That's correct.

21 DR. McCULLEY: Thank you.

22 Are there any other questions?

23 (No response.)

24 DR. McCULLEY: I think what we'll do I have

1 roughly 1:00. Let's take about a 35-minute lunch break and
2 reconvene here at 1:35.

3 (Whereupon, at 1:00 p.m., the meeting was
4 recessed for lunch, to reconvene at 1:35 p.m.)

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AFTERNOON SESSION

(1:50 p.m.)

1 DR. McCULLEY: I think we should begin. Can I
2 please have everyone's attention and have everyone back to
3 the table?

4 As I see it, I can categorize our remaining
5 responsibilities into at least three categories. One is we
6 have to make a recommendation, or we're asked to make a
7 recommendation relative to this PMA. We have a list of
8 written questions from the FDA, and I'm sure we have some
9 issues that we wish to discuss among ourselves that would
10 relate to our responses to the other two.

11 What I'd first like to do, just to have in the
12 record, would be to have Ms. Thornton read to us the panel
13 recommendation options for premarket approval applications.

14 MS. THORNTON: Good afternoon. The Medical
15 Device Amendments to the Federal Food, Drug and Cosmetic
16 Act require that the Food and Drug Administration obtain a
17 recommendation from an outside expert advisory panel on
18 designated medical device premarket approval applications
19 that are filed with the agency. The PMA must stand on its
20 own merits, and your recommendation must be supported by
21 safety and effectiveness data in the application or by
22 applicable publicly available information.

23 "Safety" is defined in the Act as "reasonable
24 assurance based on valid scientific evidence that the

1 probable benefits to health under the conditions of use
2 outweigh any probable risks." "Effectiveness" is defined
3 as "reasonable assurance that, in a significant portion of
4 the population, the use of the device for its intended uses
5 and conditions of use, when labeled, will provide
6 clinically significant results."

7 Your recommendation options for the vote are as
8 follows:

9 Approval, meaning there are no conditions
10 attached.

11 Agency action. If the agency agrees with the
12 panel recommendation, an approvable letter will be sent to
13 the applicant.

14 The second option is approvable with
15 conditions. You may recommend that the PMA be found
16 approvable subject to specified conditions, such as
17 resolution of clearly identified deficiencies which have
18 been cited by you or by the FDA staff. Prior to voting,
19 all of the conditions are discussed by the panel and listed
20 by the panel chair. You may specify what type of follow-up
21 to the applicant's response to the conditions of your
22 approvable recommendation you want. For example, just FDA
23 or panel follow-up, which is characteristically done by
24 homework assignment. Panel follow up is usually done by

1 these homework assignments to the primary reviewers of the
2 application but may be to other specified members of the
3 panel. A formal discussion of the application at a future
4 panel meeting is not usually held.

5 If you recommend post-approval requirements to
6 be imposed as a condition of approval, then your
7 recommendation should address the following points: the
8 purpose of the requirement, number of subjects to be
9 evaluated, and reports that should be required to be
10 submitted.

11 If FDA agrees with the panel recommendation, an
12 approvable with conditions letter will be sent.

13 The third option is not approvable. Of the
14 five reasons that the Act specifies for denial of approval,
15 the following three reasons are applicable to panel
16 deliberations: the data do not provide reasonable
17 assurance that the device is safe under the conditions of
18 use prescribed, recommended, or suggested in the proposed
19 labeling; reasonable assurance has not been given that the
20 device is effective under the conditions of use prescribed,
21 recommended, or suggested in the labeling; based on a fair
22 evaluation of all the material facts in your discussions,
23 you believe the proposed labeling to be false or
24 misleading.

1 If you recommend that the application is not
2 approvable for any of these stated reasons, then we ask
3 that you identify the measures that you think are necessary
4 for the application to be placed in an approvable form.

5 If FDA agrees with the panel's not approvable
6 recommendation, we will send a not approvable letter. This
7 is not a final agency action on the PMA. The applicant has
8 the opportunity to amend the PMA to supply the requested
9 information. The amended application will be reviewed by
10 the panel at a future meeting unless the panel requests
11 otherwise.

12 In rare circumstances, the panel may decide to
13 table an application. Tabling an application does not give
14 specific guidance from the panel to FDA or the applicant,
15 thereby creating ambiguity and delay in the progress of the
16 application. Therefore, we discourage tabling of an
17 application. The panel should consider a not approvable or
18 approvable with conditions recommendation that gives
19 clearly described corrective steps. If the panel does vote
20 to table a PMA, the panel will be asked to describe which
21 information is missing and what prevents an alternative
22 recommendation.

23 Following the voting, the chair will ask each
24 panel member to present a brief statement outlining the

1 reasons for their vote.

2 Thank you, Mr. Chairman.

3 DR. McCULLEY: Thank you.

4 Are there any strong feelings about the
5 progress that anyone would like to state at this point as
6 to where we should go next? We have three options. We can
7 open the floor to discuss among ourselves what we think the
8 direction should be, we could entertain a motion in that
9 regard, or we can begin to address the FDA questions as
10 they have been posed to us.

11 DR. BULLIMORE: I propose that we address the
12 questions in a swift fashion, but keep in mind when we're
13 addressing them that they may end up becoming conditions.
14 But I think until we've gone through what is essentially a
15 work order --

16 DR. McCULLEY: Is there consensus on that?
17 Marian, you're shaking your head.

18 DR. MACSAI: No.

19 DR. McCULLEY: What is your recommendation?

20 DR. MACSAI: Yes, I am shaking my head. I
21 guess the question is whether or not this is even
22 approvable in my mind, at this time, with or without
23 conditions. So, if it's not, why would we go through this
24 list of questions?

1 DR. McCULLEY: Well, our options are approval,
2 approvable with conditions, or not approvable, and as I
3 read this, that doesn't say rejection, it's just not
4 approvable in its current form. Or we could table. Those
5 are the four options available to us. Now, do we want to
6 pick the direction we're going in and then fine-tune with
7 detail, or do we want to work around the details and
8 finally come into a final decision? I suppose that partly
9 depends on the present feelings of the panel, whether
10 there's a consensus or not, and I don't know quite how
11 we're going to come to that.

12 Dr. Ruiz?

13 DR. RUIZ: Mr. Chairman, I make a motion that
14 we approve this with conditions that we will outline after
15 we take this vote.

16 DR. McCULLEY: Is there a second?

17 DR. VAN METER: I will second it.

18 DR. McCULLEY: Is there further discussion
19 prior to vote on that?

20 Dr. Ferris?

21 DR. FERRIS: I'm not a voting member, but I
22 wonder if it wouldn't be better to at least have a little
23 discussion before we vote on a motion.

24 DR. MACSAI: I'm in agreement with Dr. Ferris.

1 I have a level of discomfort with the accountability in
2 this PMA. I'm uncomfortable with not knowing the true
3 complication rate with repeated enhancements. I'm
4 uncomfortable in not knowing the side effects the patients
5 will experience after this procedure.

6 DR. McCULLEY: Okay. Then what you're stating
7 is that you're not comfortable voting at this point one way
8 or the other without additional discussion.

9 DR. RUIZ: Mr. Chairman, we're having the
10 discussion now. We're having discussion of the motion
11 right now. Go ahead and discuss.

12 DR. MACSAI: Right, and I can't set out
13 conditions. Don't we have to lay out the conditions before
14 we vote on your motion, Dr. Ruiz?

15 DR. RUIZ: Well, yes. But if you feel strongly
16 about it, you'll have to vote against the motion.

17 DR. ROSENTHAL: You can discuss the motion.
18 You can begin to have your discussions. Without taking a
19 vote, you should discuss your --

20 DR. McCULLEY: Yes, and have the conditions
21 laid out on which the vote would then be made.

22 Dr. Higginbotham?

23 DR. HIGGINBOTHAM: I'll try and get off this
24 dime for us. I guess one of my concerns and something that

1 I'd like to put forth as a possible condition is the
2 patient satisfaction, or at least some indicator that could
3 be used to assess how well patients do with this procedure
4 postoperatively. Certainly the sponsor can consider using
5 the questionnaire that they put forth in their packet but
6 capture a greater proportion of the patients than what they
7 have currently captured, perhaps considering six months as
8 another time point. But perhaps we could have a discussion
9 about that, and I'd like to perhaps hear Dr. Ferris in
10 terms of what his opinion might be.

11 DR. FERRIS: Mr. Chairman, I have some comments
12 which I'd like to make, if I could.

13 DR. McCULLEY: Please.

14 DR. FERRIS: First, I would like to direct
15 these comments not just to this specific proposal but also
16 to future LASIK proposals. Apparently the FDA is going to
17 require us to start voting instead of just kibitzing, so
18 with that in mind, I'd like to at least get my opinion on
19 the table.

20 I would like to congratulate the presenters of
21 this particular -- what's it called?

22 DR. McCULLEY: PMA?

23 DR. FERRIS: PMA. They've done a remarkable
24 ~~job for an investigator initiated clinical research~~

1 project. In fact, I think it's phenomenal considering they
2 had no support other than what they generated themselves.
3 So to the extent that I'm saying anything negative, I hope
4 they understand that I think they've done a fabulous job.

5 However, our job, as I see it, is to look at
6 efficacy, and as I see this, is there any effect or is this
7 a placebo, and what's the variability of that effect,
8 what's the variance, and then safety. I think it's not
9 possible to think that this is a placebo. There's
10 obviously an effect. So the questions left are what about
11 the variability of the effect, long-term issues as well as
12 short-term, and safety. What I'd like to try to do is
13 differentiate between science and clinical impression.

14 The fact of the matter is that both Dr. Waring
15 and Dr. Thompson are known to me and to others to be
16 serious clinical researchers and honest people, and from
17 that point of view, I take what they say very seriously and
18 believe what they say. But if we have to hold this up to a
19 scientific assessment, at least I have a major problem, and
20 that is that what I call losses to follow-up, or
21 accountability I think was the other term that was
22 discussed this morning, is a major issue here.

23 Unfortunately, as we've seen in previous applications, this
24 ~~is a common problem for myopia treatment studies.~~

1 The participants with myopia do not consider
2 themselves to be sick, and certainly don't consider
3 themselves to need long-term care. So unlike diabetic
4 retinopathy, where we fairly readily can get only 2 percent
5 loss to follow-up, it's much more difficult here, and I
6 recognize that.

7 How can we scientifically adjust for losses to
8 follow-up? There's a favorite quote, for clinical
9 trialists at least, that says, "The only way to
10 scientifically deal with losses to follow-up is not to have
11 any." Other clinical trialists say you need to take a
12 conservative approach, and the conservative approach is
13 that you take all losses to a follow-up and count them as
14 bad outcomes. Well, I think that's a little extreme. I
15 think Dr. Waring is right, that probably the vast majority
16 of the people that have not come back have not come back
17 because they're doing fine, they don't see any reason to
18 come back. The problem is we don't have any way of knowing
19 whether that's true or not. In fact, we have a little
20 snippet of information that says 10 percent of the people,
21 when asked about satisfaction, said they weren't satisfied.
22 I'm not exactly sure of the numbers, but I guess if you
23 looked at 10 percent of 45 percent, that would be 4.5
24 ~~percent who aren't coming back because they're dissatisfied~~

1 and maybe they had a bad outcome.

2 I think we need some sort of better information
3 on what's happened to those people. I think maybe we have
4 to be creative in terms of losses to follow-up. One of the
5 things that can be done is to look and see whether those
6 lost are somehow different from those who are continued to
7 be followed either based on baseline characteristics or
8 possibly last visual acuity before they were lost, and
9 perhaps there's other information.

10 Now, one of the things that I've been struck
11 with in thinking about the treatment of myopia is that my
12 view of it is that these people aren't sick. They have
13 options for the treatment of their myopia, one of which is
14 glasses, which has some side effects but nothing very
15 serious, and now they have other options. The subject of
16 assessment here I think is maybe critically important.
17 That's not to say that I don't want objective findings too,
18 but these people choose this treatment because they have
19 certain goals in mind, and whether they've achieved those
20 goals or not seems to me to be very important.

21 I don't think the patients particularly care
22 about the objective assessment. I think they care about
23 why they paid whatever it is, thousands of dollars for
24 this, did they get their money's worth. And the only way I

1 know how to assess this is to try to get some sort of
2 fairly long-term subjective assessment. I'd even be happy
3 with one-year assessment at this point. But what I'd like
4 to see is some sort of accountability, like we have a
5 subjective report from 90-plus percent of our population.

6 I think George made a good point, that he would
7 like to -- Dr. Waring made a good point when he said that
8 there are a lot of questions that are critically important
9 to understanding the direction of future research in this
10 area, and I encourage him to get that information. But the
11 kind of information that I'm interested in is a lot less
12 detailed than that. What I would like to see is a shorter
13 questionnaire that gets at the nub of how these patients
14 assess how they're doing.

15 If I had my first choice, I'd not have their
16 doctors find out, because I think patients like to please
17 their doctors. I'd sort of like an independent assessment,
18 and I wouldn't be unhappy with a telephone survey or some
19 other approach such as that. As I mentioned earlier, the
20 NEI is currently working on a myopia visual function type
21 questionnaire. I'm not suggesting that this necessarily
22 has to await the development of that, although there may be
23 enough already engendered that they could at least talk to
24 those investigators and use the nub of that. I think

1 they've already had the -- what do they call these little
2 touchy-feely conferences where people tell --

3 PARTICIPANT: Focus groups?

4 DR. FERRIS: Focus groups, yes. Excuse me.

5 (Laughter.)

6 DR. FERRIS: I think they've had the focus
7 group part of that, and maybe some of that information
8 would be useful.

9 Thank you, Mr. Chairman.

10 DR. McCULLEY: Thank you.

11 Other comments? Judy?

12 DR. GORDON: Judy Gordon. I'd just like to
13 comment, and I thought about saying this earlier, but I
14 think since accountability has come up as such a
15 significant issue --

16 DR. McCULLEY: Could you speak more into the
17 mike?

18 DR. GORDON: Since accountability has come up
19 as such a significant issue in the study, and it is in
20 every study, I do want to point out that although the
21 protocol that was laid out and approved under the IDE did
22 call for a 12-month follow-up -- is that correct? I'm
23 assuming that that was the case. Current FDA guidance
24 indicates and requires only a six month follow up with

1 LASIK studies.

2 DR. McCULLEY: LASIK -- is that correct? It's
3 PRK.

4 DR. GORDON: No, 12-month for PRK and six
5 months for LASIK, and that consensus was reached, and that
6 information has been discussed by this panel, as well as by
7 a working group consisting of surgeons from the different
8 associations, FDA, and industry members, and that was, to a
9 large extent, based on data that existed, whether or not
10 published, but existing also within FDA and within the
11 experience from other sponsors of LASIK studies that there
12 is early stabilization of LASIK, earlier than of PRK. In
13 fact, the current requirement of the 12-month follow-up for
14 PRK has been decreased from five or six years ago from the
15 early studies.

16 So I think as the base of knowledge builds, the
17 guidance is adapted to that. I'm interjecting this only to
18 point out that with good intentions and at the time the
19 study was started, a one-year follow-up was required, but
20 I'm confident that there are sponsors who are currently
21 planning and conducting six-month studies. So I would
22 challenge the issue of making a determination of
23 approvability of this file based on the loss to follow-up
24 or lack of good accountability at 12 months when it's not

1 required at this time.

2 DR. McCULLEY: Dr. Rosenthal?

3 DR. ROSENTHAL: Dr. Eydelman --

4 DR. GORDON: Please correct me if I'm
5 inaccurate in my statements.

6 DR. ROSENTHAL: No, you're correct. But Dr.
7 Eydelman just pointed out that the next question you would
8 have is what was the accountability at six months.

9 DR. McCULLEY: It was on the tip of my tongue.
10 What was the accountability at six months?

11 DR. ROSENTHAL: Sixty-eight percent at six
12 months.

13 DR. McCULLEY: Thank you.

14 DR. FERRIS: That was my comment. My comments
15 still hold. Whether the hurdle is six months or 12 months,
16 my comments hold that right now we don't have anything like
17 90 percent follow-up at either of those times.

18 DR. McCULLEY: And 90 percent has been set as
19 the standard. Is that correct?

20 DR. FERRIS: That's my standard.

21 DR. McCULLEY: But the FDA in the guidance
22 document has it set at 90 percent.

23 DR. GORDON: Ninety percent is generally an
24 acceptable standard. But if six months is acceptable, and

1 if the number is 68 percent, and particularly the patients
2 that are in the later group, the Group 2, there's an
3 opportunity at this time because they've only been enrolled
4 since last September, they're coming to their six-month
5 gate, that data should be forthcoming shortly. So I think
6 the sponsor has every opportunity to have excellent
7 accountability and to implement a questionnaire at that
8 six-month window, and perhaps that information would be
9 more pertinent than trying to go back and improve six- and
10 12-month follow-up on the larger group of patients with the
11 nomogram that is not going to be followed.

12 I think probably one of the concerns about the
13 lack of information on glares, halos, et cetera, is that I
14 think there is interest on the part of the panel and, in
15 the future, on the part of patients in comparing across
16 procedures. So you do have other manufacturers who have
17 asked these kinds of standard questions so patients have an
18 idea of what to expect. But I'm saying this also given
19 that it's not too late certainly for you to still get a
20 good cohort of information of that nature, and it can be
21 done quite simply. And shorter, in fact, is better. We
22 certainly have that experience with questionnaires.

23 DR. McCULLEY: As a point of clarification from
24 the FDA, with the six months having been set in the

1 guidance document, I would assume that that presumes
2 demonstration of stability leading into six months. So
3 it's not six months -- whack. It's a provisional six
4 months, depending on the demonstration of stability.

5 DR. GORDON: Correct.

6 DR. McCULLEY: And no other outstanding issues.

7 DR. EYDELMAN: That decision was made assuming
8 three months stability for LASIK.

9 DR. BULLIMORE: I'd like to build on the
10 comments made by Dr. Ferris and Dr. Gordon. In any
11 investigation like this, whether it's under the purview of
12 the FDA or the NEI, there are three things, I think, that
13 an investigator needs to do. They need to choose the right
14 measure, they need to measure it carefully, and they need
15 to measure it in the follow-up windows that were specified
16 in the protocol. What we're faced with in this particular
17 case is some deficiencies, some of which may have been
18 foreseeable, some of which are unforeseen, in each of these
19 three categories. And I think as a panel, we need to
20 identify where the serious deficiencies are and how we can
21 remedy them.

22 For example, the plan, if you like, to poll the
23 patients at 12 months is a deficiency of planning, because
24 ~~if six months is good enough to win, then in retrospect the~~

1 sponsor should have administered the questionnaire at six
2 months. Having said that, the device that they're using is
3 clearly overkill in terms of the volume of questions that
4 have been put to the patient. Shorter questionnaires that
5 have been proposed by other people on this panel, including
6 Dr. Higginbotham, would probably serve them better.

7 I'm struggling, as is Dr. Macsai and, no doubt,
8 other people on the panel, about what course of action to
9 take here now. I think at the moment, if I can say how I'm
10 feeling, I think approvable with conditions is something I
11 could vote for, but I think I would like to see some more
12 data either reviewed internally by the FDA or as a homework
13 assignment to sort of increase the accountability. I think
14 that's the fatal flaw at the moment, the accountability.

15 DR. RUIZ: That will be one of the conditions.

16 DR. BULLIMORE: Okay. But until we know what
17 the conditions are --

18 DR. HIGGINBOTHAM: Dr. Chair, can we go through
19 the conditions?

20 DR. McCULLEY: We can.

21 Are there other comments? Dr. Rosenthal, you
22 look like you have something.

23 DR. ROSENTHAL: It's just that Dr. Macsai
24 brought out some interesting questions. I mean, you're all

1 moving in the direction of patient questionnaire. There's
2 no question about that, or I don't think there's much
3 question.

4 What I would like from the panel is some idea
5 of some of the issues you would like to have addressed in a
6 revised questionnaire, if you feel a revised questionnaire
7 is in order, when you reach that point.

8 DR. MACSAI: I think, if I may quote the
9 sponsors, it would be nice to compare apples with apples
10 and not apples with oranges. If other refractive
11 procedures have measured certain things, then this
12 refractive procedure should also measure those things.
13 However, I do applaud Dr. Waring and Dr. Thompson for
14 looking at this contact lens thing and glasses thing
15 because I want to know. I want to know the answers to this
16 questionnaire, but not if it means I'm not going to get the
17 data that lets me compare this technique with other
18 techniques that are options for these patients.

19 DR. ROSENTHAL: Thank you.

20 DR. McCULLEY: Other comments at this point, or
21 would you like to go through the questions from the FDA?

22 DR. BULLIMORE: Questions.

23 DR. McCULLEY: Okay. "The PMA presents data on
24 1,545 eyes which underwent only LASIK as a primary

1 procedure. 840 of these eyes were treated with the
2 original nomogram and 705 with the revised nomogram.
3 Follow-up data at 12 months is submitted for 205 eyes
4 treated with the original nomogram. Follow-up data on eyes
5 treated with the revised nomogram is available for 352 eyes
6 at three months and 22 eyes at six months. The applicant
7 is requesting PMA approval for the revised nomogram only.

8 "The sponsor has not submitted a refractive
9 stability analysis for the eyes treated with the revised
10 nomogram. Analysis of refractive stability for the eyes
11 treated with the original nomogram demonstrate that for 95
12 percent of the eyes, the refractive change between three
13 and six months is within +1.42/-1.47 diopters, and between
14 six months and 12 months within +1.38/-1.27 diopters.
15 Current refractive guidance for myopia less than 7.0
16 diopters defines refractive stability as a change of less
17 than or equal to 1.0 diopter of manifest spherical
18 equivalent refraction between two refractions for 95
19 percent of the eyes treated.

20 "A. Has adequate refractive stability been
21 demonstrated with the original nomogram at six months and
22 at 12 months?"

23 Two questions. The first question is, has
24 refractive stability been demonstrated with the original

1 nomogram at six months?

2 DR. RUIZ: Well, since the percentage of
3 follow-up or the percent of loss to follow-up is pretty
4 high, I guess the answer is no.

5 DR. MACSAI: Not only that, if we don't know
6 the 12-month data, how can we tell if it's stable at six
7 months?

8 DR. McCULLEY: Three to six.

9 DR. RUIZ: We're not setting new criteria here,
10 though. We're not setting new criteria.

11 DR. McCULLEY: To establish it at six months,
12 presumably one would look at three months and six months.

13 DR. MACSAI: Okay. I was jumping on it. I'm
14 sorry. I was talking about the 12 months.

15 DR. RUIZ: So you've got 60 percent of 70
16 percent --

17 DR. EYDELMAN: There's 41 percent loss to
18 follow-up.

19 DR. RUIZ: Forty-one percent loss to follow-up.
20 So the answer is going to be no because there's not enough
21 follow-up.

22 DR. McCULLEY: Dr. Ferris?

23 DR. FERRIS: In addition to the follow-up
24 ~~problem, as Dr. Waring mentioned this morning, it is~~

1 surprising to I guess everyone that there is as much
2 variability in both directions here, and I'm sure they're
3 interested in trying to get to the bottom of that because
4 this is beyond what one would expect. I know they don't
5 have sloppy refractionists there, so this is something more
6 than that, and it's something that isn't understood, and
7 some more work needs to be done here.

8 DR. McCULLEY: And based on guidance numbers,
9 it does not look like it -- I mean, it's there in black and
10 white, so it's hard to deny.

11 At 12 months the answer would be the same. So
12 the answer to both parts of that question in A, the answers
13 are no.

14 Is there any disagreement with that?

15 DR. FERRIS: One other comment. Although I
16 think accountability is critical here, I think we have to
17 be reasonable in terms of what's possible, and I suspect
18 that it may be virtually impossible in the United States of
19 America to get 90 percent of these people back at a year.
20 So I don't think that we should be demanding that.

21 On the other hand, if they could show me that
22 the people who didn't come back were just as satisfied,
23 more or less, as the people that did come back, I'd be
24 willing to take the objective data from the group that you

1 had and say, well, we can't be sure, but as a group, the
2 people who weren't followed were similar in baseline
3 characteristics, were similar in visual acuity at last
4 visit, and were similar in their subjective assessment.
5 Then I think we ought to take the objective data that we
6 have to be adequate. If they're different, then all bets
7 are off.

8 DR. VAN METER: We have data, and I guess our
9 concern is, is this data going to vary if we get completed
10 data at 12 months.

11 DR. McCULLEY: What I hear Dr. Ferris saying is
12 that you would look at those patients that have not
13 returned for follow-up, do an analysis of a segment of
14 those to determine if their outcomes are similar to those
15 that did return for follow-up, and if they are, assume that
16 they're representative of the total group.

17 DR. FERRIS: That's what I'm saying.

18 DR. MACSAI: If they're subjective --

19 DR. RUIZ: Mr. Chairman, we can ask ourselves
20 these questions over and over and over again. The simple
21 fact is that the loss to follow-up is too great, so that
22 the data aren't any good for anything, for any answer.
23 What Rick is saying is that he would accept these data if
24 he gets a subjective indication that the patients are happy

1 and satisfied, which really isn't that difficult to do over
2 the telephone or with a short form.

3 DR. McCULLEY: Dr. Macsai?

4 DR. MACSAI: Dr. Ruiz, if you're that unhappy,
5 then why do you want it approved with conditions?

6 DR. RUIZ: I have my reasons.

7 DR. MACSAI: Could you share them with me?

8 DR. RUIZ: Yes, because I think the procedure
9 is very effective, I think it's very safe, and I'm pretty
10 convinced. Now, when you just look at it from a purely
11 statistical standpoint, there is too much loss to follow-up
12 here for this data to be really meaningful. But they've
13 got a chance now with the second group, Group 2, which they
14 have their three-month follow-up on 300-something cases, so
15 they can get another set of data that's good. They can
16 redo this survey, which is much, much, much too
17 complicated. They can even do it on the telephone,
18 probably with a 5- to 10-minute interview and satisfy me
19 that there aren't any big catastrophes walking around out
20 there.

21 DR. BULLIMORE: Just to support what Dr. Ruiz
22 says, we recently completed a whole series of VF14 and VFQ
23 questionnaires on the phone to elderly low-vision patients.
24 ~~The mean administration time for the VF14 was 9 minutes;~~

1 the mean administration time for the VFQ, which is 25
2 questions, was closer to 18 minutes. This is doable. It's
3 a question of going out and doing it.

4 DR. RUIZ: And if we get up there to 80 percent
5 or so of all the patients and we get those kind of
6 responses, then we're satisfied.

7 DR. McCULLEY: I'm hearing -- I don't know if
8 it's a mixed message, a complimentary message or what. Dr.
9 Ferris proposed that the patients in Group 1 who are not
10 accounted for at the moment could be polled. Dr. Ruiz just
11 proposed that instead of doing that, that the solution to
12 this, a more appropriate solution to this would be to wait
13 and get six-month data, and hopefully with good
14 accountability and a questionnaire on Group 2 patients.
15 Those two are very different, and those two, I would think,
16 would influence in a very different way the panel's
17 recommendation.

18 DR. FERRIS: But I'm not unhappy with the
19 concept of trying to get total follow-up on the Group 2,
20 maybe even more than the 68 percent information at six
21 months, and trying to get 90 percent information at least,
22 subjective information. That would satisfy me too. In
23 fact, Group 2 is more relevant here because that's what
24 we're being asked to assess.

1 DR. McCULLEY: But we don't have six-month data
2 on Group 2.

3 DR. FERRIS: We can't get it now.

4 DR. RUIZ: The issue is they have to get it.

5 DR. McCULLEY: Okay. The B to this question:
6 "FDA has recently recommended that the sponsor analyzes
7 separately stability data for eyes with refractive error
8 below -7.0 diopters of myopia for ease of comparison to our
9 refractive guidance. Does the panel feel that a breakdown
10 of stability data into subsets zero to -7.0 and greater
11 than 7.0 allow them to better evaluate the outcomes of this
12 device?"

13 I heard from a couple of panel members in
14 discussions that they'd like to see stratification even
15 finer than in those two broad areas. Sponsor presented
16 data on -7.0 and below, which we saw for the first time
17 today.

18 DR. BULLIMORE: With respect, Mr. Chairman, I
19 don't believe they actually presented stability data for
20 those particular subgroups, either of them. I will stand
21 corrected.

22 DR. VAN METER: The data that we got on zero to
23 7.0 was a best possible case scenario of patients with
24 20/20 potential acuity and less than 1.0 diopter of

1 astigmatism. Those patients that had greater than 7.0
2 diopters were lumped in with a group of patients that had
3 up to 22.0 diopters. So both of these are muddy, if you
4 will.

5 DR. MACSAI: I think further stratification
6 would be of benefit both in analysis of the data on the
7 panel's part and in analysis of the data on the patient's
8 part.

9 DR. McCULLEY: So is the panel recommendation
10 that patients be stratified in one to two diopter groups,
11 from -1.0 to -15.0?

12 DR. RUIZ: How burdensome is that?

13 DR. MACSAI: I don't care.

14 DR. McCULLEY: The question is do we want to
15 see it or not?

16 DR. BULLIMORE: I don't want to see that.

17 DR. McCULLEY: You do or you don't?

18 DR. BULLIMORE: No.

19 DR. RUIZ: No, I don't either.

20 DR. MACSAI: I do.

21 DR. RUIZ: I think up to -7.0, and from -7.0 up
22 to 15.0 would be very interesting and useful.

23 DR. FERRIS: One of the problems with
24 stratifying into too small a group is that the variability

1 within groups is going to be so large that it's going to be
2 uninterpretable if you do see differences.

3 DR. McCULLEY: What stratification would you
4 recommend? Two broad groups, or more than two?

5 DR. FERRIS: I think the group that they did up
6 to 7.0, and actually I kind of liked the matching
7 eligibility criteria with the PRK data because then there
8 was a benchmark to compare it with. You were, as they were
9 saying, comparing apples with apples. I would want to see
10 the actual frequency distributions, and I know I've seen
11 them but I don't have them memorized. I would demand that
12 the group be large enough that I could say something about
13 it, although it may be, since they're not even asking for
14 anything above 15.0, I would look at that group separately.

15 Whether you look at 7.0 to 15.0, which is a
16 pretty broad group, or divide it into two pieces, which
17 might be useful, I think that's about as fine as you could
18 cut that pie and come up with any kind of reasonable
19 ability --

20 DR. McCULLEY: Divide the 7.0 to 15.0 into two
21 groups.

22 DR. FERRIS: Divide them into two groups, with
23 the idea of trying to look to see is there any indication
24 that there are increased risks or benefits in the higher

1 group compared to the lower group.

2 DR. McCULLEY: So the suggestion would be that
3 the answer to B is yes, but in the group that is above
4 -7.0, to divide the -7.0 to -15.0 into two groups.

5 DR. FERRIS: And then a third group since I
6 guess they still have data even in Group 2 on greater than
7 15.0. Are there any patients in there? Anyway, that's a
8 separate group, and if they're in there, they need to show
9 us what happened to them.

10 DR. McCULLEY: Is there consensus on the 1.0 to
11 7.0, and then the 7.0 to 15.0 divided into two groups? And
12 if there's sufficient data on above 15.0, for interest to
13 provide that? Is there any disagreement to that?

14 DR. RUIZ: Let me ask the sponsors if they
15 think that's a useful -- or can I ask the sponsors?

16 DR. McCULLEY: No, you can't.

17 DR. RUIZ: I think we should be cognizant of
18 not just making work.

19 DR. VAN METER: Does it make any difference
20 between 7.0 and 15.0 if there's a subset? I mean, are we
21 looking for anything?

22 DR. FERRIS: The only concern that I have is
23 one related to as you get to higher and higher myopia,
24 ~~maybe the cornea is thinner, the potential for side effects~~

1 might be greater in the higher myopes than the lower
2 myopes.

3 DR. RUIZ: It would show up, though, in the
4 second group, wouldn't it? Over the first group.

5 DR. FERRIS: It may or may not.

6 DR. McCULLEY: It depends. We don't know
7 whether the safety cutoff for upper limits of LASIK is
8 13.0, 14.0, 15.0, or 17.0. It could be anywhere in there,
9 and if we don't have data in those areas, then we don't
10 know where the safety cutoff should be.

11 DR. RUIZ: They did a bunch of work and they
12 cut it off themselves at 15.0 for a reason.

13 DR. McCULLEY: They didn't present the reasons
14 to us. So without those reasons, we really can't make an
15 objective evaluation.

16 DR. RUIZ: I don't have any objection to
17 breaking it up into two groups from 7.0 to 15.0, Mr.
18 Chairman.

19 DR. FERRIS: Actually, from the point of view
20 of statistical analysis, since I do this all the time, I'm
21 sure their statisticians aren't worried about that. You
22 can always lump them back together, and I think they should
23 be lumped together. I just think for some of the analyses
24 ~~it would be good to look at them stratified just to make~~

1 certain that there isn't anything going on.

2 The reason that I'm concerned that you might
3 miss something, to answer Dick's point, is that these bad
4 outcomes that we're talking about look like they're quite
5 rare. From the data that I see, I suspect that at the end
6 of the day we're going to find out that side effects are
7 pretty uncommon, and because they're uncommon, if they are
8 clumped toward the end, they'll be lost. They're going to
9 be harder to see because they'll be swamped out by the fact
10 that most of the patients are between 7.0 and 10.0 or 10.5,
11 not 10.5 to 15.0.

12 DR. McCULLEY: Ms. Thornton has an announcement
13 to make.

14 MS. THORNTON: Excuse me, Dr. Chairman.

15 Oh, I'm doing it now. I'm sorry.

16 (Laughter.)

17 MS. THORNTON: I just wanted to announce to
18 those people who have some concerns about the questions and
19 seeing them on the screen, Mr. Calogero has left and is
20 returning momentarily, we hope, with the projection pad so
21 that the audience will be able to see the questions.

22 DR. McCULLEY: Thank you.

23 DR. RUIZ: Mr. Chairman, where is the break
24 point on the second category, from 7.0 to 15.0?

1 DR. MACSAI: Eleven.

2 DR. McCULLEY: I think we were probably leaving
3 that loose and giving them some flexibility so they can see
4 how the numbers fall.

5 DR. MACSAI: Halfway.

6 DR. FERRIS: They may have to cut it in half in
7 order to have big enough groups to look at it.

8 DR. McCULLEY: Or it may not be in half.

9 DR. FERRIS: Half in terms of population.

10 DR. McCULLEY: Okay. "C, Is the current
11 definition of refractive stability in the guidance
12 appropriate for studies with higher myopic error?"

13 DR. HIGGINBOTHAM: Insufficient information.

14 DR. MACSAI: We don't have data to make --
15 unless I misunderstood how the data was presented, it
16 wasn't presented in a way that we can answer this question.

17 DR. McCULLEY: This is more of a generic
18 question. Is the current definition of refractive
19 stability in the guidance appropriate for studies with
20 higher myopic error?

21 DR. MACSAI: Oh, sorry.

22 DR. McCULLEY: This is stability.

23 DR. BULLIMORE: What is the current guidance?

24 DR. McCULLEY: ~~It's stated up here as 1.0~~

1 diopter of manifest spherical equivalent for refraction
2 between two refractions for 95 percent of the eyes treated.

3 DR. RUIZ: This is the first time this has ever
4 even been looked at, so obviously we don't have guidelines
5 on that.

6 DR. McCULLEY: In the guidance there is a
7 guideline for refractive stability that has been accepted
8 as our standard.

9 DR. RUIZ: I know, but there's nothing to
10 support that, right?

11 DR. McCULLEY: It's still the guidance. It was
12 based on best opinion and best knowledge at the time. It
13 is in the guidance. Do we think that is what it should be,
14 or do we think it should change for the higher degrees of
15 myopia? We're talking about stability now, we're not
16 talking about predictability. We're talking about
17 stability of the cornea after it has been treated. Is
18 there any reason to accept that a cornea with higher
19 degrees of myopia can have less stability? It says within
20 two refractions for 95 percent of the eyes.

21 DR. RUIZ: When they finish this study, we may
22 have something to base our judgment on.

23 DR. BULLIMORE: I say yes to the question.

24 DR. McCULLEY: The current definition is

1 appropriate for studies in higher degrees of myopia.

2 Other opinion? Judy?

3 DR. GORDON: Judy Gordon. We had a little bit
4 of this discussion --

5 PARTICIPANT: Can you speak louder?

6 MS. THORNTON: Can you speak louder, Judy?

7 DR. GORDON: Yes. Judy Gordon. We've had this
8 discussion previously relative to all of these measures for
9 the higher levels of myopia because the guidance covers up
10 to -7.0, what's currently accepted for PRK. I think I'll
11 comment again today, as I have before, that it's very hard
12 to define these things in the abstract, as one given
13 parameter, because I do think there's an overall
14 risk/benefit ratio that varies. So maybe a little bit less
15 stability is offset by a greater benefit to the patient or
16 greater satisfaction.

17 It's just so hard to arbitrarily establish
18 those kinds of things without having the bigger picture of
19 all of the outcomes.

20 DR. BULLIMORE: I agree partly with you, but I
21 think in terms of refractive stability, it doesn't matter
22 where you started. If you're an emmetrope wobbling around
23 by plus or minus 2.0, then it shouldn't matter where you
24 started.

1 In terms of predictability of a procedure, yes,
2 I think an accuracy of plus or minus 2.0 diopters, if
3 you're starting at -15.0, is perhaps acceptable, whereas an
4 outcome of plus or minus 1.0 is more appropriate if you
5 start at a -5.0. But in terms of stability and quality of
6 vision, I'd be very nervous about making the guidelines any
7 different for people who start higher in refractive error.

8 DR. McCULLEY: So I think possibly the answer
9 to this would be in the absence of data to support one
10 direction or the other. We would be uncomfortable in
11 changing or making a recommendation to deviate.

12 DR. ROSENTHAL: The other issue is that you can
13 state this, and if the data comes in at 1.14 but 99 percent
14 of the patients are elated, I don't think anybody is going
15 to say you have to meet the 1.00.

16 DR. GORDON: And that was my point.

17 DR. ROSENTHAL: Yes, I know that. Nor will the
18 FDA turn down an application because it didn't meet 1.00.

19 DR. McCULLEY: So did we effectively address C
20 for the time being?

21 DR. ROSENTHAL: Yes, I think you have.

22 DR. McCULLEY: Okay. D, "Based on the
23 refractive stability presented in this PMA, is the current
24 ~~follow up of eyes treated with revised nomogram sufficient~~

1 to provide reasonable assurance of safety and effectiveness
2 for this device?"

3 DR. RUIZ: No.

4 DR. McCULLEY: Does anyone disagree with that
5 response?

6 (No response.)

7 DR. McCULLEY: The answer is no.

8 DR. MACSAI: Can I add to that, or do you want
9 us to not discuss it anymore?

10 DR. McCULLEY: It's pretty self-evident; they
11 don't have six-month data.

12 DR. MACSAI: Well, I also would say that we
13 need more information on follow-up on the incidence of
14 complications with repeated enhancements, which are
15 starting at the three-month point, and at six months we'll
16 only have three-month follow-up on those enhancements, so
17 that may not be enough.

18 DR. BULLIMORE: I think that's going to be
19 taken care of in Question 4. I don't think we should jump
20 ahead too quickly here.

21 DR. MACSAI: Okay.

22 DR. McCULLEY: Number 2. "For ease of
23 comparison to our current refractive guidance, FDA has
24 ~~recently recommended that the sponsor analyze separately~~

1 all safety and efficacy endpoints for eyes with refractive
2 error below -7.0 diopters of myopia. The agency has not
3 received or reviewed this stratified analysis." I think
4 that's the analysis pretty much that we heard today.

5 "FDA's review is based only upon the safety and
6 effectiveness outcomes of the full range of myopia from
7 -1.0 to -15.0."

8 "A" under this is, "Is a stratified analysis of
9 these data critical to a recommendation of reasonable
10 assurance of safety and effectiveness of the applicant's
11 device?" I think we've already answered that in the
12 affirmative.

13 "What, if any, additional data analyses are
14 needed to make the decisions?" I think we've also
15 addressed that and we would break the -7.0 and above into
16 two groups, or recommend that, for analysis.

17 DR. MACSAI: Also, what about attempted versus
18 achieved?

19 DR. McCULLEY: The question is to include
20 attempted versus achieved. I would hope that they would do
21 that if they're aiming for monovision.

22 DR. MACSAI: Or purposely undercorrecting.
23 It's nice to know if the device achieves what it attempts.

24 ~~DR. McCULLEY: Well, we know they're scoting~~

1 up on it, and that's the attempt they're taking so as to
2 avoid overcorrection. But even with that, in Group 2,
3 there was 1.2 percent that were greater than 2.0 diopters
4 overcorrected.

5 DR. MACSAI: Right. So that's why it would be
6 important to look at attempted versus achieved.

7 DR. McCULLEY: Number 3 --

8 DR. ROSENTHAL: Excuse me. What is the sense
9 of the panel relating to that?

10 DR. McCULLEY: We already answered those.

11 DR. ROSENTHAL: Relating to intended versus
12 achieved?

13 DR. McCULLEY: We've agreed.

14 DR. ROSENTHAL: You've agreed? I'm sorry. I
15 beg your pardon.

16 DR. McCULLEY: You're right, I had not gotten
17 the head nods.

18 DR. ROSENTHAL: You agreed by nodding your
19 heads, but I like to hear it.

20 DR. McCULLEY: Number 3. "Do the testing
21 results on contrast sensitivity, glare, and topography
22 provide reasonable assurance of safety and effectiveness of
23 this device?"

24 DR. MACSAI: No.

1 DR. BULLIMORE: No.

2 DR. McCULLEY: I'm hearing no's from everyone.
3 Is there disagreement to that?

4 DR. VAN METER: I have a question, because the
5 topography data was inconclusive and there was no
6 particular correlation or information to be gleaned from
7 it. In the contrast sensitivity data, there was both a
8 loss and a gain, and I'm not sure that it appears to
9 change. It sort of permeates the data and doesn't show any
10 particular significance to low errors or higher refractive
11 errors, and I'm not sure how you could get more information
12 out of this.

13 DR. McCULLEY: Topography was only presented on
14 patients that had greater than two or more loss of best
15 corrected. The wording of the question is, "Do the testing
16 results on contrast sensitivity, glare, and topography
17 provide reasonable assurance of safety and effectiveness of
18 this device?"

19 DR. MACSAI: No.

20 DR. FERRIS: Is the no because of missing data,
21 or is the no because within the data that we saw, we
22 thought there was a problem?

23 DR. MACSAI: Within the data that we saw, we
24 ~~thought there was a problem.~~

1 DR. RUIZ: It's still no.

2 DR. McCULLEY: I agree, but I think we do need
3 to clarify what we mean by no, and it's probably a little
4 bit of both, that it was not helpful and that some of it
5 raised questions.

6 DR. MACSAI: Well, the glare data, for example,
7 didn't quite make sense, and I would presume that's due to
8 lack of long-term follow-up on Group 2, but I don't know.
9 So I can't make a decision on that.

10 DR. ROSENTHAL: The other issue is
11 stratification.

12 DR. McCULLEY: Stratify this data?

13 DR. ROSENTHAL: Well, the issue is you have a
14 bulk of data and we're not sure, right? Now, it may be
15 that at the end of the process we're still not sure, but
16 it's worth trying to find out whether or not, within
17 certain levels of myopia, they experience more difficulty
18 than at other levels. So if you find out that they don't,
19 then you'll come back and you'll say it hasn't helped at
20 all, but at least you've tried to prove it one way or the
21 other.

22 DR. McCULLEY: I don't think we have the data
23 to say what you just said. We don't know. The data was
24 ~~not presented in a manner that we could say~~

1 DR. MACSAI: Perhaps we should then stratify it
2 and look at it again.

3 DR. McCULLEY: I think the answer to the
4 question is no. We recommend that the sponsor stratify
5 their data and try to put it in a meaningful form for us.

6 DR. MACSAI: And get more of it on the follow-
7 up.

8 DR. ROSENTHAL: There's also an issue on
9 topography. I have to ask the panel what their feeling is
10 about topographic data. I think the other is pretty
11 straightforward in that you have numbers and you can crunch
12 them out, but with topography, there was a controversy
13 between the sponsor and us about what to submit, and we
14 finally agreed to have just the topographical data on the
15 patients who lost two or more lines of best corrected
16 visual acuity.

17 DR. SUGAR: The data presented doesn't allow us
18 to draw conclusions either way. I don't think that there's
19 enough -- there's plenty of information there, but I don't
20 think that there's enough correlation between the
21 information provided and the outcomes that it's meaningful
22 to us. So I personally don't think we need to ask for more
23 topographic information.

24 ~~DR. BULLIMORE: I would agree with that and~~

1 extend that to the glare data. I think the contrast
2 sensitivity data is the only one of the three that I would
3 be interested in looking at in a stratified manner.

4 DR. VAN METER: But are you interested in
5 having it on the good results, or should they continue to
6 just do it on the patients with --

7 DR. BULLIMORE: Contrast sensitivity on the
8 whole cohort, and I want to see it stratified because it
9 may be that when we do the high and the low myopic groups,
10 the pattern will be that it's the high myopes that lose
11 contrast sensitivity and the low myopes that gain it, or
12 vice versa.

13 DR. McCULLEY: Is the consensus that we only
14 want stratified data on contrast sensitivity?

15 DR. RUIZ: Yes.

16 DR. MACSAI: No.

17 DR. McCULLEY: It's not? State your view.

18 DR. BULLIMORE: Yes.

19 DR. RUIZ: Yes.

20 DR. McCULLEY: Okay, we have a yes.

21 DR. MACSAI: And we have a no.

22 DR. McCULLEY: And we have a no. I'm asking
23 you to state your view.

24 DR. MACSAI: I would like some understanding of

1 the glare testing results that the sponsors couldn't
2 explain either. If the testing is going to be done and
3 data obtained, we should have some understanding of what it
4 shows, because it wasn't sufficiently obtained on Group 2.

5 DR. McCULLEY: Is there agreement that we want
6 glare testing as well stratified? Anyone opposed to that?

7 (No response.)

8 DR. McCULLEY: So the consensus is that we wish
9 to see stratified data on contrast sensitivity and glare.

10 DR. MACSAI: Either Dr. Sugar or Dr. Van Meter
11 had something that they said during their review about
12 topography.

13 DR. McCULLEY: He did, and he just --

14 DR. MACSAI: You reversed that decision? I
15 don't remember what you said, if you could --

16 DR. McCULLEY: The point is he's not asking for
17 it now. He's saying that he does not think it's going to
18 be of benefit.

19 DR. MACSAI: Is that because they haven't
20 analyzed it on the people with good results? Or why?

21 DR. SUGAR: It just didn't appear to be
22 sufficient correlation between the topographic analyses and
23 the outcomes to make it meaningful.

24 DR. McCULLEY: It appeared to be an unhelpful

1 tool.

2 DR. FERRIS: As opposed to contrast
3 sensitivity, for example, which has been so useful to us in
4 all these other studies we've done over the years.

5 (Laughter.)

6 DR. FERRIS: I think it's fine to try to
7 continue to collect data on glare and contrast sensitivity.
8 I would not hold the sponsors responsible for explaining
9 this data because I think that the most that they can be
10 held to do is to provide it. If there are questions, they
11 may be research questions for further work. But I don't
12 think we can hold them to explain it, because I haven't
13 been able to explain any contrast sensitivity data I've
14 ever seen.

15 DR. McCULLEY: Fair enough. As I still hear
16 it, the consensus is that we wish to have stratified data
17 on contrast sensitivity and glare.

18 DR. ROSENTHAL: May I just take this one step
19 further, Mr. Chairman? And that is to say, do you feel
20 that topographic analyses are no longer even necessary?

21 DR. McCULLEY: I'm not sure I'm completely
22 comfortable with throwing that out. I don't think it was
23 helpful with the data that they presented, but I don't
24 think we know enough yet to know that it's not, and I'm not

1 100 percent sure we ought not to ask them, the sponsor in
2 this case, to try to make some sense of the topographic
3 data.

4 DR. ROSENTHAL: Do you feel a sample of the
5 good results might be worth analyzing? Or do you totally
6 feel that -- I mean, if you don't feel it's of any value,
7 then it's of no value at all, and why are we asking people
8 to do it?

9 DR. SUGAR: It may be of value if they derive
10 indices that they didn't derive, like irregularity indices.

11 DR. FERRIS: I think if they had had lots of
12 complications, the topographical data might have been very
13 useful. The fact that they had so few events, at least to
14 me, made the topographical information not very useful
15 because there wasn't any way of really correlating them.

16 DR. McCULLEY: Possibly we could ask for a
17 matched group of good outcomes compared to those who had
18 the difficult outcomes, to see what kind of comparison we
19 might see with that, to get some idea of what kind of
20 information we might look for in the future.

21 DR. BULLIMORE: We're back to what Dr. Ruiz
22 characterized earlier as busy work for the sponsor. I
23 don't think it's going to impact our decision. Yes, it
24 would be interesting. I would love to sit down and look at

1 the contrast sensitivity data, but --

2 DR. ROSENTHAL: The issue has to do with
3 approvability of their PMA. We cannot require companies to
4 do research because we might find it interesting. It has
5 to be relevant to the application we're looking at and
6 important to a decision you're going to make about safety
7 and effectiveness.

8 DR. McCULLEY: It also brings the issue up that
9 you stated a minute ago, do we now want topography, period.

10 DR. FERRIS: But those are different. They've
11 done a lot of topography, and I think they've demonstrated
12 in their study that it isn't useful. That doesn't mean
13 that when the next study comes in, I don't want to at least
14 see the same thing that allows me to say, gee --

15 DR. ROSENTHAL: I apologize for even bringing
16 it up.

17 DR. McCULLEY: So let me restate the consensus
18 as I heard it. Correct me if I'm wrong. We are requesting
19 contrast sensitivity and glare data to be presented in a
20 stratified manner.

21 DR. RUIZ: Not any new data, just the data they
22 already have.

23 DR. McCULLEY: The data they have. Is that
24 correct? Does that state the sense

1 DR. MACSAI: I thought they were going to get
2 it on Group 2 when they come in for their follow-up? I
3 misunderstood. What are we requesting?

4 DR. McCULLEY: That's one of the problems that
5 I got back to before, that we're dealing with Group 1 with
6 poor accountability, we've got Group 2 without
7 accountability. Relative to accountability, Dr. Ferris
8 suggested an approach to try to deal with that on Group 1,
9 and that is going to muddy the whole issue and it's going
10 to stay muddied as long as we have two or three issues on
11 the table.

12 DR. MACSAI: Well, then collect the data on
13 Group 2 which is going to have good accountability. They
14 want approval of the Group 2 nomogram.

15 DR. McCULLEY: That would lead to a different
16 kind of recommendation from the panel from where we were,
17 where we were going.

18 DR. SONI: Can we limit it to just glare and
19 not do contrast sensitivity on Group 2? Because that's the
20 important outcome measure that you want to look at from a
21 patient's point of view.

22 DR. MACSAI: So is low contrast vision.

23 DR. BULLIMORE: Isn't there a point of protocol
24 here? The sponsor is operating under an IDE which was

1 approved by the FDA. Is it really the panel's
2 responsibility to say, well, you don't need to take all
3 that data? I think they should continue taking it.
4 Whether we want to see it at a future date or as homework
5 assignments, or whether we want the FDA to pay attention to
6 it as part of our conditions for approval, that's another
7 matter. But if they're operating under an IDE and
8 collecting data, then they should continue to do so.

9 DR. ROSENTHAL: I presume on Group 2 you have
10 to collect the same data you've collected on Group 1. So
11 your recommendation is to stratify what you have and
12 collect what you're expected to collect in your follow-up
13 studies.

14 DR. McCULLEY: That makes sense.

15 Dr. Gordon?

16 DR. GORDON: Judy Gordon. I did want to
17 comment, and I actually got a useful note from someone in
18 the audience reminding me, because I don't keep in my head
19 all of the definitions in the current guidance. But it has
20 been made clear that sponsors can address issues of
21 contrast and glare in their labeling without doing the
22 studies needed to establish that there is no loss of
23 contrast.

24 So, again, their study was initiated before

1 this guidance went into effect, and just in an attempt to
2 maintain an even playing field, I think it's inappropriate
3 to require data from them that, one, is difficult to
4 interpret and understand, and I think on a number of
5 occasions this panel has taken the position that we don't
6 know what it means and it hasn't been raised in reviews of
7 previous PMA's, and, two, is not any longer required.

8 DR. McCULLEY: Dr. Drum?

9 DR. DRUM: I'd like to qualify what you've
10 said.

11 DR. GORDON: Please.

12 DR. DRUM: I think the conditions under which
13 the contrast sensitivity studies are not required are those
14 where we have some understanding of outcomes based on
15 previous studies. But if there are new conditions where we
16 suspect that there may be problems with contrast
17 sensitivity, we may ask for the studies rather than just
18 the labeling.

19 DR. McCULLEY: Can we leave this now with the
20 FDA to try to sort this out? I would only say I would not
21 expect any new issues with contrast sensitivity or glare
22 with LASIK as opposed to PRK.

23 DR. DRUM: But with high refractive errors,
24 there may be.

1 DR. McCULLEY: Number 4. "Which of the
2 following two options does the panel feel is the
3 appropriate endpoint for the comparison to safety and
4 effectiveness targets outlined in our refractive guidance:
5 A) Safety and effectiveness results after the primary
6 refractive correction only; or, B) Outcomes after all
7 enhancements?"

8 DR. VAN METER: B.

9 DR. McCULLEY: Dr. Van Meter says B.

10 DR. VAN METER: I would like to state B because
11 I think that the safety results will not be known until
12 after all enhancements, and the effectiveness data will not
13 be accurate until after all enhancements.

14 DR. McCULLEY: But we also have to know how
15 many enhancements there are.

16 Dr. Ferris?

17 DR. FERRIS: But I think it's relevant that the
18 sponsors this morning said that when they present this to
19 their patients, they present it as a package. At least it
20 seems to me the assessment ought to be at the end of the
21 package. I understand that there's a time issue here and a
22 follow-up question, but I think for at least some of these
23 things, it needs to be looked at as a package, just like
24 all of the pieces — there are four different pieces of

1 this -- are part of the same package.

2 DR. McCULLEY: So it would be after all
3 enhancements? Consensus on that? Yes?

4 DR. MACSAI: Yes.

5 DR. RUIZ: Yes.

6 DR. BULLIMORE: Yes.

7 DR. McCULLEY: Okay. Number 5. "The sponsor
8 has requested approval of their device for simultaneous
9 LASIK surgery."

10 DR. MACSAI: You skipped one.

11 DR. McCULLEY: I did? Oh. "Is your
12 recommendation appropriate for all future LASIK devices?"
13 I'm sorry.

14 DR. MACSAI: Yes.

15 DR. RUIZ: Yes.

16 DR. BULLIMORE: Yes.

17 DR. McCULLEY: Thank you.

18 Number 5. "The sponsor has requested approval
19 of their device for simultaneous LASIK surgery. How does
20 the panel feel the data regarding simultaneous surgery
21 should be presented in the labeling?"

22 DR. SUGAR: It should not be.

23 DR. FERRIS: Can I ask why that's even an
24 issue?

1 DR. MACSAI: Yes, I thought Malvina said that
2 it was not being requested at the very beginning.

3 DR. ROSENTHAL: It was requested.

4 DR. MACSAI: I must have misunderstood.

5 DR. FERRIS: But isn't it a matter of --

6 DR. RUIZ: Practice of medicine.

7 DR. McCULLEY: She said this was a -- as I
8 recall, it's not part of the approval. It would be part of
9 the labeling, if I recall the statement and am restating it
10 accurately.

11 DR. RUIZ: Why should it be on the label?

12 DR. McCULLEY: Why should it be on the label,
13 Dr. Ruiz asks.

14 DR. MACSAI: Practice of medicine.

15 DR. McCULLEY: Practice of medicine. Our
16 response will be the panel's response I guess. They're
17 asking us for a response, then, and they're passing that on
18 to us. So practice of medicine?

19 DR. SUGAR: Same for the next question.

20 DR. McCULLEY: Let's take them one at a time,
21 and we can ditto it if it is the same.

22 DR. ROSENTHAL: Do you feel that the data
23 should be presented in the labeling but no recommendation

24 made? Do you feel no data at all should be put in the

1 labeling about the simultaneous?

2 DR. McCULLEY: I heard a comment down here.

3 Would you like to restate it, Dr. Ruiz?

4 DR. RUIZ: My feeling would be that nothing
5 should be put in there.

6 DR. McCULLEY: Dr. Sugar?

7 DR. SUGAR: I agree.

8 DR. VAN METER: I agree.

9 DR. McCULLEY: Is there any dissent to that?

10 (No response.)

11 DR. McCULLEY: So the response to that is that
12 the issue of bilateral, simultaneous, same setting,
13 whatever we're going to call it, should not be addressed in
14 the approval or the labeling.

15 Number 6. "The sponsor has requested approval
16 for monocular surgery," et cetera. You can read it on the
17 board.

18 Dr. Sugar suggested that this was the same.

19 DR. ROSENTHAL: Excuse me. Do you want him to
20 read it into the record?

21 MS. THORNTON: Yes.

22 DR. ROSENTHAL: Would you please read it, Dr.
23 McCulley?

24 DR. McCULLEY: Okay.

1 DR. ROSENTHAL: Sorry.

2 DR. McCULLEY: That's all right. I'll get you
3 later.

4 "The sponsor has requested approval for
5 monocular surgery. In this PMA, monocular surgery was
6 defined as surgery on one eye of a patient which was
7 performed for one of the following reasons: 1)
8 Anisometropia secondary to previous surgery leaving
9 residual myopia in one eye; 2) Patient wanting a surgery
10 in one eye only to retain monovision in the unoperated eye
11 for near work; 3) Patient capable of affording surgery in
12 one eye only. How does the panel feel the data regarding
13 monocular surgery should be presented in the labeling?"

14 I heard a ditto to our previous one. Is there
15 consensus on that, or further discussion? Consensus?

16 DR. GORDON: Meaning --

17 DR. McCULLEY: Meaning it should be left out of
18 the labeling.

19 DR. MACSAI: It should not be put in.

20 DR. McCULLEY: Question 7. "A subjective
21 patient satisfaction questionnaire was administered to all
22 subjects in this study at the 12-month visit."

23 Well, not all.

24 (Laughter.)

1 DR. McCULLEY: "However, no psychometric data
2 were submitted to FDA. The sponsor is planning to submit
3 the results of the questionnaire after all subjects
4 complete the 12-month examination. Will the results of
5 patient questionnaire influence the panel's recommendation
6 regarding approval of this device?"

7 There's a specific question there: Will the
8 results of the patient questionnaire influence the panel's
9 recommendation regarding approval of this device?

10 DR. MACSAI: Yes.

11 DR. VAN METER: Absolutely.

12 DR. McCULLEY: Unanimous yes.

13 I would like to ask Dr. Ferris to state briefly
14 what he views the consensus of the panel to be relative to
15 what should be done about a meaningful patient
16 questionnaire that we would like to see submitted.

17 DR. FERRIS: Well, that's a tall order.

18 DR. McCULLEY: I can take it back.

19 DR. FERRIS: I think that the questionnaire
20 items that I'm the most interested in are items such as --
21 if I had nothing other than Question 37 on 95 percent of
22 people, I would feel a lot better about the safety and
23 efficacy of this. Question 37 I believe says something
24 like "Are you satisfied with this?" From very satisfied to

1 very dissatisfied. At the end of the day, with these
2 questionnaires oftentimes those global questions turn out
3 to be as good as all the little pieces.

4 I would only stress that I think the
5 questionnaire should be short enough so that it could be
6 acceptable to the vast majority of the population, that the
7 focus is on these questions on the safety and effectiveness
8 from the patient's point of view, and I encourage the
9 sponsors to go ahead and do other questionnaires on a
10 subset that they can get their hands on that are willing to
11 spend the hour and a half to get the further information
12 that they need to advance this procedure. But the one that
13 I'm talking about is the one that we can get information on
14 virtually everybody.

15 DR. ROSENTHAL: And, I might add, from the FDA
16 standpoint, one which we request from other sponsors for
17 similar refractive surgical procedures.

18 DR. FERRIS: I didn't say that before, but I
19 would like to certainly go on the record as saying that I
20 would hope that we could get some sort of benchmark set of
21 questions that we would hold all applications to so that we
22 are comparing apples with apples. If they want to expand
23 upon that subset of questions, that's fine, but there's at
24 least a core that everybody does.

1 DR. McCULLEY: There are a couple of issues
2 that --

3 DR. ROSENTHAL: Mr. Chairman, excuse me. May I
4 just go back to one issue, which is Question 4. You have
5 said that you feel it's appropriate that the endpoint for
6 comparison of safety and effectiveness targets are the
7 outcomes after all enhancements. Do you want to set a time
8 limit?

9 DR. FERRIS: I'd like to address part of that.

10 DR. ROSENTHAL: Could you just address that
11 issue for us and give us a sense of the panel's feeling
12 about "after all"?

13 DR. FERRIS: All is almost impossible if
14 they're dribbling on. What it looked like to me, and
15 perhaps the sponsor can address this with the agency, is
16 that after six months or some such date, that 90-plus
17 percent of any further enhancements -- you've got all the
18 enhancements that you're going to have except for a number
19 dribbling in. One could look at the data, for example, and
20 do some analysis that says, well, even if we looked at this
21 last 5 or 10 percent, it could hardly change the overall
22 view of the data.

23 I suspect there is a second safety question,
24 ~~though, and that is one that nobody would know the answer~~

1 to, and that is can you just keep doing this forever? Can
2 you do four or five or ten? That's a second question.

3 DR. EYDELMAN: I just wanted to point out that
4 on the next part of this question -- i.e., is this
5 appropriate for all future LASIK devices? -- you have voted
6 yes. I'm trying to translate this into realistic
7 expectations for future LASIK sponsors. How long before
8 endpoints are considered endpoints?

9 DR. BULLIMORE: I think the safety issue should
10 be for all enhancements. I think we should, for future
11 proposals, say maybe after one enhancement, that we should
12 evaluate efficacy after one enhancement and, let's face it,
13 if they're not getting within 85 or 90 percent after one
14 enhancement, then maybe it's not a good procedure.

15 DR. MACSAI: How many enhancements before you
16 consider it a failure? When do you stop?

17 DR. McCULLEY: You could go on forever and if
18 there was some way to deal with overcorrections --

19 DR. MACSAI: If they look at 2,000 patients,
20 and two patients need three enhancements, should those two
21 patients hold up the whole PMA? I don't think so. But we
22 need to know if 20 percent of the patients are going to
23 need two enhancements, or what are the results after two.

24 DR. McCULLEY: I think we want to know the

1 frequency of enhancements -- one, two, and so on.

2 Dr. Ferris?

3 DR. FERRIS: From a practical point of view,
4 keeping in mind what Dr. Gordon said, it would seem to me
5 that anybody who was providing information better have in
6 mind that they're going to need something like a year
7 follow-up to deal with the fact that there are probably
8 going to be multiple enhancements and that it won't be
9 enough to just say we have six-month data, which means we
10 only have three-month data on most of the enhancements.
11 They're going to have to have some sort of longer-term
12 follow-up if they're going to be enhanced.

13 Now, if they have a procedure that doesn't need
14 any enhancements, then six-month data would be okay.

15 DR. MACSAI: And the other thing would be if
16 there are lots of enhancements and a few patients, you
17 could just do postmarket surveillance to see what's -- I
18 know you're rolling your eyes, but you can't hold up a
19 whole thing over two patients.

20 DR. McCULLEY: We have gone through the
21 questions. There is a motion that has been seconded on the
22 floor. Some of the issues we went through I think we
23 reached an endpoint on. We did not on stability in that we
24 felt that stability apparently could not be finalized

1 without knowing more what the data was, whether to go with
2 the limits in the guidance document.

3 Is there further discussion on the motion on
4 the floor?

5 DR. HIGGINBOTHAM: Yes.

6 DR. McCULLEY: Dr. Higginbotham.

7 DR. HIGGINBOTHAM: Dr. Chair, I'd like to offer
8 another consideration. Considering that there is such a
9 lack of diversity in this cohort, and we heard yesterday
10 that there are racial differences that might exist between
11 African Americans and Caucasian Americans, and I believe
12 that there might be some differences in the PRK data as
13 well, that the investigators be encouraged to add to the
14 minority subgroup in this cohort.

15 DR. McCULLEY: Dr. Waring, I'm ignoring you on
16 purpose for the moment.

17 I need clarification, please, as a new chair,
18 as to whether people from the audience, including sponsor,
19 approaching the podium should be allowed back into the
20 proceedings.

21 DR. WARING: I would just like to respond to
22 some of the questions that have been raised --

23 DR. McCULLEY: Excuse me one second, George. I
24 need guidance because I don't know what to do. I'm trying

1 to be fair and appropriate, so forgive me.

2 MS. THORNTON: My guidance is that it is at the
3 discretion of the chair at this point.

4 DR. McCULLEY: Dr. Waring?

5 MS. THORNTON: There's nothing stated that
6 forbids it. It's according to how you feel the proceedings
7 are going, whether there was a direct question that was
8 posed to the sponsor and he was asked to respond.

9 DR. McCULLEY: George, may I ask you to state
10 your purpose in approaching the podium?

11 DR. WARING: Yes. My purpose is to try to
12 respond in three or four sentences to some of the questions
13 that have been raised based upon our Group 1 database.

14 DR. McCULLEY: Please.

15 DR. WARING: I would like to remind the panel
16 of the one slide that we showed where we demonstrated the
17 eyes that lost two or more lines of spectacle corrected
18 acuity, and we demonstrated that only three of those eyes
19 lost worse than 20/40, two of which had retinal
20 complications. Those eyes represent all of the eyes,
21 1,040-odd eyes, in the database at the last examination.
22 So while we realize that our follow-up at six months is
23 less than we would all like, we have provided to you that
24 ~~follow up, whether it's 24 hours, two weeks, or one year,~~

1 on all of the eyes, and only three of them lost vision down
2 to that particular level.

3 DR. McCULLEY: George, if you have comments
4 that relate to things that were up, that was not one of our
5 outstanding issues still that was unclear to us.

6 DR. WARING: The reason I brought it up is that
7 our accountability is less than desirable, and I was trying
8 to make the point that we did look at all of the eyes over
9 the entire time to report those data.

10 DR. McCULLEY: Thank you.

11 Is there further discussion on the motion that
12 has been seconded on the floor?

13 DR. BULLIMORE: I'd like to actually list the
14 conditions before we vote on this. That would be my
15 preference, but I understand it's the chair's prerogative
16 to do anything else.

17 DR. McCULLEY: Oh, no. I'm happy to. In terms
18 of accountability, the condition was that the sponsor do
19 one of two, or both, provide analysis of the patients that
20 were not accounted for to demonstrate whether they are
21 representative of the patients that are accounted for or
22 whether they represent a different group. If they are
23 representative, that that be acceptable data; and/or that
24 ~~six month data be obtained on Group 2 patients with good~~

1 accountability.

2 I would like clarification from the panel
3 whether that is an "and" or an "or."

4 DR. BULLIMORE: I would like to have some
5 definition of what is good accountability. I think it's in
6 the sponsor's best interest and the FDA's best interest --

7 DR. McCULLEY: The guidance document says 90
8 percent. I think that would still be our benchmark, that
9 we would not change that benchmark.

10 DR. BULLIMORE: So can we say 90 percent?

11 DR. McCULLEY: Yes. We can say based on the
12 guidance document. I think all our comments, unless we
13 state otherwise, would be within the parameters of the
14 guidance document. Now, my question is, is that condition
15 an "and" or an "or" on the Group 1 and the Group 2?

16 DR. HIGGINBOTHAM: Or.

17 DR. McCULLEY: Or.

18 Are all in agreement with it being subset
19 analysis of Group 1 that have not been accounted for, et
20 cetera, and/or six-month follow-up with good accountability
21 on Group 2, with acceptable data? Is it one or the other,
22 or both?

23 DR. RUIZ: Mr. Chairman, are we saying that
24 ~~they can do a telephone survey of those who are unaccounted~~

1 for and that's going to satisfy us?

2 DR. McCULLEY: That is not what I heard Dr.
3 Ferris to say. He would want to see assurance that the
4 group that had not been accounted for was not different
5 from the group that had been fully evaluated.

6 DR. RUIZ: My question is, can this be done
7 subjectively or are they going to have to drag all those
8 patients back in and check them?

9 DR. FERRIS: The reason that I suggested that
10 perhaps the phone survey would be adequate is because I
11 think if we demand them to get --

12 DR. RUIZ: I think the phone survey would be
13 adequate. I'm just trying to get the chairman to say that
14 that's what we're saying to them.

15 DR. FERRIS: If they would be willing to -- and
16 I take Judy's point, that it may be easier for them to
17 start now and try to get as many as possible in for the
18 six-month visit and do some subjective questionnaire,
19 either there or --

20 DR. RUIZ: On Group 2.

21 DR. FERRIS: On Group 2, and then for the
22 people that they just can't get in, then at least get a
23 telephone questionnaire giving us some sense of security
24 that there aren't any disasters lurking out there, that

1 that's adequate.

2 DR. McCULLEY: So I hear that a telephone
3 survey on the Group 1 unaccounted for is what is
4 recommended, or --

5 DR. RUIZ: Do they have to get up to 90 percent
6 on that survey?

7 DR. FERRIS: They have to get to 90 percent
8 someplace, and it may be easier for them to get it in the
9 Group 2.

10 DR. RUIZ: So it might be easier for them just
11 to analyze their second group and get the data in better
12 shape.

13 DR. McCULLEY: So, to restate it, it is a
14 survey of the unaccounted for patients, bringing total
15 accountability up to at least 90 percent, with that
16 telephone survey giving an assurance that those that have
17 not been accounted for to date do not represent a different
18 population than those who have been accounted for; and/or
19 six-month data with good accountability on Group 2
20 patients.

21 PARTICIPANT: Just plain "or."

22 DR. McCULLEY: The consensus is "or"?

23 DR. MACSAI: I would vote for "and."

24 DR. McCULLEY: There's one "and." Are there

1 any other "ands"?

2 (No response.)

3 DR. McCULLEY: The "or's" have it.

4 Now, that is one condition on accountability.

5 Do you want further clarification?

6 DR. HIGGINBOTHAM: I'd like to remind the panel
7 that of the patients that returned for their 12-month
8 visit, they did not get 100 percent.

9 DR. McCULLEY: That's their problem.

10 DR. HIGGINBOTHAM: So we might define the
11 patients -- 90 percent of all the patients that physically
12 come back for their --

13 DR. McCULLEY: No, it's a telephone survey. It
14 was stated as I said, and they may have --

15 DR. HIGGINBOTHAM: Okay, fine.

16 DR. McCULLEY: We can state what we wish. We
17 can't exactly tell people how to solve the issues.

18 The other question was stability, and we hedged
19 on that one. We said no, that stability had not been
20 demonstrated because of the lack of accountability and
21 because of the lack of stability. We hedged on whether the
22 guidance should be changed in the higher degrees of myopia
23 in the absence of data. So we have a condition relative to
24 stability that I guess we have to state clearly in a

1 recommendation for approvable. Would anyone like to make
2 an attempt at that?

3 DR. BULLIMORE: I'll offer an alternative, that
4 that just be included in the labeling as a warning. I
5 think this is a tough one since collecting data on the
6 outstanding 30 percent of patients isn't probably going to
7 do much to the variability. So if we say the variability
8 has to come down, we're probably setting them an
9 unreasonable goal.

10 DR. RUIZ: They might be able to do it in Group
11 2.

12 DR. McCULLEY: It could be done in Group 2.
13 For additional data on stability, we're not going to get
14 anything more from Group 1, I don't think, realistically.

15 DR. BULLIMORE: That's why I propose --

16 DR. McCULLEY: In Group 2 we would.

17 Dr. Ferris?

18 DR. FERRIS: It seems to me critical that if we
19 had the data that it seems we're asking for with regard to
20 patient outcome, subjective outcome, the fact that the
21 guideline says plus or minus 1.0 diopter, as Ralph said
22 earlier, may be satisfied with plus or minus 1.5 because we
23 don't have any sense of disaster here.

24 DR. RUIZ: Mr. Chairman, is it the feeling of

1 the panel that a warning on the label about fluctuations is
2 sufficient?

3 DR. MACSAI: No, it's not a consensus.

4 DR. McCULLEY: I don't sense that either, but
5 we need to be able to state clearly what our condition
6 relative to stability is.

7 DR. MACSAI: The sponsor establishes stability,
8 not the panel.

9 DR. McCULLEY: If we are giving approvable with
10 conditions, we need to state what our recommendation is
11 relative to the stability that we would like to see
12 achieved for our approvability recommendation to be carried
13 forward. It's difficult because we have data that is not
14 within the stability guidance.

15 DR. FERRIS: That's what I wondered. I mean,
16 there is a guidance there which says plus or minus 1.0
17 diopter. We have some flexibility, and I suspect we might
18 feel quite different if we had data on 90 percent of the
19 patients that said they were happy with this, and there was
20 a question on there that said, "Is your vision changing
21 throughout the day?" and 90 percent said no. If 90 percent
22 said yes, then I would feel differently than if 90 percent
23 said no. So without the data, I don't know how to respond
24 to it.

1 DR. McCULLEY: Well, it's very difficult.

2 DR. MACSAI: So how can you set up a condition
3 for approval?

4 DR. McCULLEY: I'm asking someone to tell me.

5 DR. HIGGINBOTHAM: Can we suggest perhaps plus
6 or minus 1.5? We were told that of the people they
7 sampled, there was 90 percent patient satisfaction.

8 DR. McCULLEY: This one is plus or minus 0.50.
9 It would be within 1.0 diopter, is the current guidance.
10 Plus or minus 1.0 or 1.50 would be within 3.0 diopters.

11 DR. HIGGINBOTHAM: The current data is plus --

12 DR. McCULLEY: It's 3.0 diopters.

13 DR. HIGGINBOTHAM: Three diopters. So I offer
14 that as an offering to this panel.

15 DR. BULLIMORE: I think the key word is
16 "guidance" here. It's not a mandate. It's not a statute.
17 It's guidance. As an advisory panel, we have some latitude
18 to make a recommendation based on our scientific
19 backgrounds.

20 DR. McCULLEY: And it's what are we
21 recommending to the FDA as being acceptable stability for
22 them, in turn, to accept.

23 DR. BULLIMORE: Based on the data presented, I
24 don't think we have acceptable stability. But I think

1 putting a "buyer beware" clause in the warning --

2 DR. RUIZ: One might be all right for less than
3 7.0. We may find with stratification that it's not all
4 right for greater than 7.0. I like Eve's suggestion, 1.5.

5 DR. McCULLEY: That it be within 1.5 diopters
6 for greater than 7.0? That stability be demonstrated
7 between two refractions within 1.5 for corrections greater
8 than 7.0? The data is far off from that now.

9 DR. ROSENTHAL: We're asking your advice, Sir
10 doctor.

11 (Laughter.)

12 DR. VAN METER: We could leave the guidance
13 document as plus or minus 1.0, and choose to accept this
14 data on an individual case-by-case basis.

15 DR. MACSAI: I think that's arbitrary.

16 DR. McCULLEY: One of the things that's been
17 brought up in here and one of the questions that I
18 overlooked before -- "Is your recommendation appropriate
19 for all future LASIK devices?" -- I don't think we can be
20 going in first one direction and then another. I think we
21 have to establish some consistency.

22 DR. MACSAI: And with respect, Dr. Van Meter,
23 that appears arbitrary. If you don't have sufficient
24 accountability and data that's analyzed in a way that you

1 can determine stability --

2 DR. VAN METER: I understand. But let us
3 suppose that patients over 7.0 diopters do have
4 instability. We either adhere them to this standard or we
5 change the standard. Both of those are arbitrary.

6 DR. MACSAI: Well, how about if we find out
7 first?

8 DR. McCULLEY: That makes it very difficult.
9 What can the FDA -- please help. We need to
10 try to do something that is going to be constructive and
11 helpful. There is in the guidance document for less than
12 minus 7.0 -- there is not for over minus 7.0 a specific
13 stability, and the current PMA does not reach the guidance
14 for less than 7.0.

15 DR. FERRIS: But why do we have to decide this
16 now? Whichever way this goes -- and I must say that I'm a
17 little bit confused as to the difference between accepting
18 with conditions and disapproving with conditions. It
19 sounds to me that, either way, they're going to have to
20 come back, and the only difference is whether they come
21 back to the panel or they don't. If we say they come back
22 to the panel, show us the data, show us the money --

23 (Laughter.)

24 DR. FERRIS: ~~and then we can decide that~~

1 plus or minus 1.5 -- if you had subjective assessments that
2 said people weren't in trouble, maybe you wouldn't be
3 worried about plus or minus 1.5.

4 DR. McCULLEY: Since it's very difficult to try
5 to come up with something concrete without data, and the
6 way to do that would be if we had the data, is it possible
7 in a recommendation for approvable that we leave this loose
8 for now with the request that this come back to full panel?
9 You were nodding your head before I finished my sentence.
10 Because that is a major difference between approvable and
11 -- it's not disapproval; it's not approvable in its current
12 form. As I read it, that is the major difference between
13 the two, that one comes back to panel that further allows
14 panel evaluation, and the other can be done with homework
15 where there is not group interaction.

16 DR. WAXLER: I hate to tread in this water but
17 it seems to me that we got to the earlier stability that's
18 in the guidance by looking at what was empirically
19 presented to us and to the panel. It seems to me that
20 strategy worked. We struggled through that by a lot of
21 discussion and getting to consensus. It seems to me a data
22 set was presented, it has what it has in terms of
23 stability. We can't make it into something else it isn't.
24 ~~It seems to me that when we have good accountability, we're~~

1 comfortable and, as Dr. Ferris said, we will know that that
2 is what LASIK produces for those dioptic ranges, and
3 presumably people will become comfortable with that.

4 I think the discomfort has to do with the fact
5 that we have an incomplete data set and we don't know
6 whether people are satisfied, or those who weren't
7 satisfied, we don't know what happened to them.

8 I think it may be premature to set a number
9 here, but be cognizant of the number that's already been
10 presented as a possible value that we might achieve.

11 DR. McCULLEY: So that leaves it, then, to the
12 FDA to make its assessment of your comfort level with
13 stability, and you don't need anything further from us at
14 this point, other than that in our conditions, that
15 acceptable stability be demonstrated and we leave the
16 definition of "acceptable" to you. That's how I heard what
17 you just said.

18 DR. MACSAI: No. I think when we have the
19 data, that's when --

20 DR. WAXLER: That's not what I heard me say,
21 actually.

22 (Laughter.)

23 DR. ROSENTHAL: It's what you wanted to hear
24 him say.

1 (Laughter.)

2 DR. WAXLER: I'll try to say it again. It
3 seems to me that it's a comfort level not just for the FDA
4 but also for the experts that sit here on the panel, and
5 let the data drive that comfort level, but let all the data
6 drive it. So that it's not simply a matter of us
7 arbitrarily coming to a value or you arbitrarily coming to
8 a value, but let's find out what those data are, look at
9 the full range. It may be different for the different
10 dioptic ranges as you stratify that data. That is what I
11 think I said before, but I'm not quite sure.

12 DR. McCULLEY: And what we said before was that
13 we did not think that adequate stability had been
14 demonstrated at this point.

15 MS. THORNTON: I would remind the panel that,
16 according to the procedure for approvable with conditions,
17 you can elect after the data has been gathered to see it as
18 a panel in homework assignment or designated for the
19 primary reviewers.

20 DR. ROSENTHAL: Thank you.

21 DR. McCULLEY: So the condition is that
22 acceptable stability be demonstrated. We have the guidance
23 document. We're not going to state anything arbitrary
24 beyond that point, and presumably it will be presented to

1 panel representation appropriately by FDA.

2 DR. ROSENTHAL: That you wish it to come back
3 to the panel in some form or another, or you wish members
4 of the panel to comment on it.

5 DR. McCULLEY: When you say that, you mean
6 homework assignment or --

7 DR. ROSENTHAL: Yes, or primary reviewers.

8 DR. MACSAI: Or do you mean discussion at a
9 meeting?

10 DR. McCULLEY: Does it come back as a homework
11 assignment to primary reviewers?

12 DR. ROSENTHAL: Can we come back to the panel?

13 DR. MACSAI: Yes, the full panel.

14 MS. THORNTON: All I read to you was that it's
15 not usually done at the approvable with conditions stage,
16 but if you choose to see it again, that's your choice.

17 DR. McCULLEY: Is there a consensus that we
18 would wish to see this presented to full panel? We are
19 going to be establishing a new standard.

20 DR. MACSAI: Yes.

21 DR. FERRIS: That's the thing that would bother
22 me, not so much this particular application, but this is
23 just the first, probably, of a series that we're going to
24 see. It would seem to me that if I was a primary reviewer,

1 I would not personally want to have the responsibility of
2 speaking for the rest of the panel.

3 DR. McCULLEY: Is there consensus that our
4 recommendation and our condition is that stability data be
5 brought back for full panel review?

6 DR. HIGGINBOTHAM: Isn't that tabling?

7 DR. McCULLEY: No.

8 DR. BULLIMORE: I know we weren't asked to talk
9 about the broader issue, but I want to make some statement
10 for the record which I hope will be important. This was
11 fast-tracked by Dr. Rosenthal because of what is presumably
12 becoming or would become the standard of care in refractive
13 surgery. That's an unusual step. It would also be an
14 unusual step for us to approve with conditions but ask to
15 see it again as a panel.

16 The benefit of both of those actions, both Dr.
17 Rosenthal's and the panel, if we were to do that, would be
18 that it would deliver a message to the community and the
19 patients that the FDA is trying to move things along and
20 the technique itself has been, with whatever conditions,
21 has been approved. I think that's an important statement
22 to make to the community and to the patients out there who
23 are being bombarded with information, disinformation,
24 misinformation.

1 DR. MACSAI: It's not "approved," it's
2 "approvable."

3 DR. BULLIMORE: Oh, I'm sorry. I stand
4 corrected -- approvable.

5 DR. WAXLER: I think one thing needs to be
6 clear, Dr. Bullimore. I think that there may be some
7 misunderstanding. I think that when this application comes
8 before the panel and the agency, it comes before the panel
9 as the Emory Vision LASIK System. This is not
10 generalizable to the Summit lasers, it's not generalizable
11 to LASIK.

12 DR. BULLIMORE: I acknowledge that.

13 DR. WAXLER: It's making a statement about what
14 future applicants may have to deal with, and in that way
15 it's very important. But it doesn't speak to making a
16 statement about how others in their practice of medicine
17 should do it.

18 DR. BULLIMORE: I agree.

19 DR. WAXLER: I just wanted to make sure that
20 that was clear.

21 DR. BULLIMORE: I acknowledge that, and I also
22 acknowledge that the word is "approvable" and not
23 "approved."

24 DR. McCULLEY: Okay. We're going down what the

1 conditions are. What I would like to do now to make things
2 easier, since we have -- have we agreed that we wish for
3 the data, the stability data to return to panel? Is there
4 agreement on that? Yes?

5 DR. HIGGINBOTHAM: Yes.

6 DR. MACSAI: Yes.

7 DR. McCULLEY: Is there disagreement?

8 (No response.)

9 DR. McCULLEY: Therefore, all of the conditions
10 that we are requesting, just to make this easy -- do we
11 wish to have the data presented to us rather than a piece
12 here and a piece there? Is there disagreement to that?

13 (No response.)

14 DR. McCULLEY: All right. So we have
15 accountability that's going to be brought back to panel, we
16 have stability data that's going to be brought back to
17 panel, we have the condition that the data be stratified
18 minus 1.0 to 7.0 and then minus 7.0 to 15.0 divided by 2,
19 with the cutoff to be determined by the sponsor, that the
20 data on contrast sensitivity and glare be stratified, and
21 that a meaningful questionnaire be completed and brought
22 back -- all of those things to be brought back to full
23 panel.

24 ~~DR. MACSAI: And the complication rates of the~~

1 enhancements.

2 DR. McCULLEY: The complication rates of the
3 enhancements.

4 DR. VAN METER: Mr. Chairman, could you please
5 resolve the conflict between having satisfaction data on a
6 12-month questionnaire when stability is thought to be
7 established in six months? We ought to either have the
8 questionnaire at six months or require stability data to
9 12.

10 DR. McCULLEY: Okay. Stability data, again,
11 just to be certain so we don't get the wrong thing stated
12 and restated, six months was assuming that stability was
13 demonstrated at six months. So it's not an absolute cutoff
14 at six months. So I think the questionnaire would probably
15 be tied to the time point when stability had been
16 demonstrated.

17 DR. VAN METER: Fair.

18 DR. McCULLEY: There's a motion to second, with
19 conditions that have been stated. Is there further
20 discussion?

21 Dr. Higginbotham.

22 DR. HIGGINBOTHAM: Dr. Chair, perhaps my
23 previous comment was lost, but I would also add that
24 ~~diversity be encouraged in the cohort.~~

1 DR. McCULLEY: I don't know that they can do
2 that in that they already have the patients enrolled.

3 DR. HIGGINBOTHAM: In Group 2? I thought they
4 were still enrolling them.

5 DR. McCULLEY: Okay, that diversity be
6 encouraged in the Group 2 cohort.

7 Any other comments?

8 (No response.)

9 DR. McCULLEY: Can I hear a call for the
10 question?

11 DR. VAN METER: I call for the question.

12 DR. McCULLEY: All in favor of the
13 recommendation for approvable with conditions, with the
14 conditions as I stated, please signify in the affirmative
15 by raising your hand.

16 (Show of hands.)

17 DR. McCULLEY: It looks unanimous.

18 PARTICIPANT: No, it's not.

19 DR. McCULLEY: Who didn't --

20 PARTICIPANT: Oh, she did.

21 DR. McCULLEY: It was a weak one, but it was
22 up. We know she's a wuss. It's hard to get that arm up
23 there.

24 (Laughter.)

1 DR. BULLIMORE: Mr. Chairman, I think that was
2 uncalled for.

3 DR. McCULLEY: I'm sorry.

4 DR. FERRIS: And if anybody on this panel's not
5 a wuss --

6 (Laughter.)

7 DR. McCULLEY: I stand reprimanded.

8 (Laughter.)

9 DR. McCULLEY: If there are no further --

10 MS. THORNTON: Oh, we have to go around and
11 poll everybody, poll them why they said yes.

12 DR. McCULLEY: Okay. We need to poll the
13 voting members to ask why they voted as they did. Please,
14 succinctly.

15 Dr. Soni?

16 DR. SONI: I voted for approvable with
17 conditions attached because I believe that we've covered
18 most of the issues that I was concerned about.

19 DR. RUIZ: I voted for approval because I think
20 when the data is cleaned up a little bit, we're going to
21 find this to be a very effective and safe procedure.

22 DR. HIGGINBOTHAM: Although I'm not happy with
23 the follow-up and the lack of patient satisfaction data, I
24 recognize that this is a significant adjunct to the

1 refractive surgery armamentarium, and certainly the
2 marketplace is begging for LASIK.

3 DR. SUGAR: I voted yes. I think that even
4 with just the data we have, it appears to be a safe and
5 effective procedure. The predictability is reasonable, the
6 stability is uncertain, and I feel we made the right
7 decision.

8 DR. VAN METER: Woody Van Meter. I voted yes.
9 As Mrs. Thornton read earlier, safety is defined as
10 probable benefits exceed probable risks, and I think that
11 has been shown by the sponsors. Effectiveness refers to
12 clinically significant results, and clearly that has been
13 demonstrated by the sponsor. I think that this technology
14 needs to be made available to the public.

15 DR. McCULLEY: Dr. Macsai?

16 DR. MACSAI: I voted yes because despite the
17 fact that there's lack of accountability and true
18 complication rates and side effects known, in fact this is
19 a well-conducted study by reliable researchers in a very
20 controlled setting, and with reexamination of the
21 stability, accountability, complication rate, and
22 effectiveness data by the panel in open session, we will
23 really be able to help the public assess what refractive
24 procedure is right for them.

1 DR. McCULLEY: Dr. Bullimore?

2 DR. BULLIMORE: I voted yes. I voiced most of
3 my concerns earlier. Accountability is obviously an issue.
4 The refractive stability has obviously not been
5 demonstrated. That comes as something of a surprise to
6 many of us, including the sponsor, but I think it's a
7 residual concern. Like many of my colleagues, I think it's
8 in the public's best interest to move this technology
9 along, and I'm happy to play a part in doing so.

10 DR. McCULLEY: The meeting is adjourned.

11 (Whereupon, at 3:40 p.m., the meeting was
12 adjourned.)

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