

UNITED STATES OF AMERICA

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FOOD AND DRUG ADMINISTRATION
MEDICAL DEVICES ADVISORY COMMITTEE

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OPHTHALMIC DEVICES ADVISORY PANEL
106TH MEETING

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FRIDAY,
OCTOBER 3, 2003

The panel met at 8:30 a.m. in the Gaithersburg Marriott Washingtonian Center, 9751 Washingtonian Boulevard, Gaithersburg, Maryland, Dr. Jayne S. Weiss, Chair, presiding.

PRESENT:

- JAYNE S. WEISS, MD., Chair
- ARTHUR BRADLEY, Ph.D., Member
- MICHAEL R. GRIMMETT, M.D., Member
- ALICE Y. MATOBA, M.D., Member
- TIMOTHY T. McMAHON, O.D., Member
- ALLEN C. HO, M.D., Member
- ANNE L. COLEMAN, M.D., Ph.D, Member
- KAREN BANDEEN-ROCHE, Ph.D, Consultant,
deputized to vote
- WILLIAM D. MATHERS, M.D., Consultant,
deputized to vote
- JOEL SUGAR, M.D., Consultant, deputized to vote
- MARIAN S. MACSAI-KAPLAN, M.D., Consultant,
deputized to vote
- JAMES P. McCULLEY, M.D., Consultant
- OLIVER D. SCHEIN, M.D., Consultant,
deputized to vote
- GLENDA V. SUCH, M.Ed., Consumer Representative
- R. MICHAEL CROMPTON, J.D., M.P.H., R.A.C.
Acting Industry Representative

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SPONSOR'S PRESENTERS:

HENRY F. EDELHAUSER, Ph.D
HELENE LAMIELLE, M.D.
DONALD R. SANDERS, M.D., Ph.D.
STEVEN G. SLADE, M.D.
JOHN A. VUKICH, M.D.

FDA PARTICIPANTS:

A. RALPH ROSENTHAL, M..D.
GERRY W. GRAY, Ph.D.
DONNA R. LOCHNER
MALVINA B. EYDELMAN, M.D.
SARA THORNTON

OPEN PUBLIC HEARING SPEAKER:

CAPT. STEVEN C. SCHALLHORN, M.D.

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

2 (8:34 a.m.)

3 DR. WEISS: Would everyone please take
4 their seats? We will be beginning in a moment. I
5 would like to call this meeting of the Ophthalmic
6 Devices Panel to order. We will have introductory
7 remarks by Sally Thornton and for the record, I would
8 like to note that there is a quorum present.

9 MS. THORNTON: Good morning. I'd like to
10 introduce myself. I am Sara Thornton, and I am the
11 Executive Secretary of the Ophthalmic Devices Panel.
12 On behalf of the FDA, I would like to welcome you to
13 the 106th meeting of the Ophthalmic Devices Panel.
14 Before we proceed with today's agenda, I have a few
15 short announcements to make. I'd like to remind
16 everyone to please sign in our at the registration
17 table. There are sheets there for you to fill out,
18 just your name and whether you're from industry or the
19 panel or FDA or the public. Please, we do like to
20 have that filled out.

21 All public handouts for today's meeting
22 are available at the registration table. There are

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1 two new additions to our usual group of handouts.
2 We've put out there information on public
3 participation in open public hearings and copies of a
4 guidance document for FDA and industry on quality
5 system information for certain pre-market application
6 reviews.

7 Messages for panel members and FDA
8 participants, information or special needs should be
9 directed through Ms. AnnMarie Williams, who is
10 available at the registration table. The phone number
11 to call for the meeting area is 301-590-0044. In
12 consideration of the panel, the sponsor and the Agency
13 we ask that those of you with cell phones and pagers
14 either turn them off or put them on vibration mode
15 while in this room and to make your calls outside the
16 meeting area, please.

17 Lastly, will all meeting participants
18 please speak into the microphone and give your name
19 clearly so the transcriber will have an accurate
20 recording of your comments? Now, at this time, I'd
21 like to extend a special welcome and introduce to the
22 public the panel and the FDA staff a new panel

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1 consultant who is with us at the table for the first
2 time today, Dr. Oliver Schein, to my left, who comes
3 to us from Johns Hopkins University where he holds a
4 joint appointment as the Grossman Professor of
5 Opthamology in the School of Medicine and as a
6 Professor of Epidemiology in the School of Public
7 Health and Hygiene.

8 His clinical expertise is in the medical
9 and surgical management of patients with corneal
10 disease and problems involving the interior segment of
11 the eye. I'd also like to welcome our acting industry
12 rep, Mr. Michael Crompton, Vice President for
13 Regulatory and Clinical Affairs and Quality Assurance
14 for Carl Zeiss Meditec, Inc. Mr. Crompton is sitting
15 in for Mr. Ronald McCarley, who will not participate
16 in today's proceedings at the request of the PMA
17 sponsor.

18 Will the remaining panel members please
19 introduce themselves beginning with Glenda?

20 MS. SUCH: Glenda Such, Consumer
21 Representative.

22 DR. SUGAR: Joel Sugar, University of

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1 Illinois at Chicago.

2 DR. BANDEEN-ROCHE: Karen Bandeen-Rhodes,
3 Johns Hopkins University.

4 DR. McMAHON: Tim McMahon, Department of
5 Ophthalmology, University of Illinois at Chicago.

6 DR. MATOBA: Alice Matoba, Cullen Eye
7 Institute, Baylor College of Medicine.

8 DR. BRADLEY: Arthur Bradley, Professor of
9 Vision Science, Indiana University.

10 DR. WEISS: Jayne Weiss, Kresge Eye
11 Institute, Wayne State University, School of Medicine.

12 DR. MATHERS: Bill Mathers, Oregon Health
13 Sciences University.

14 DR. HO: Allen Ho, Wills Eye Hospital,
15 Philadelphia.

16 DR. GRIMMETT: Michael Grimmett, West Palm
17 Beach Florida.

18 DR. MACSAI: Marian Macsai, Northwestern
19 University, Chicago.

20 DR. McCULLEY: Jim McCulley, University of
21 Texas, Southwestern Medical School, Dallas.

22 DR. COLEMAN: Anne Coleman, UCLA.

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1 DR. ROSENTHAL: Ralph Rosenthal, FDA.

2 MS. THORNTON: Thank you, panel. I'd like
3 to read now the conflict of interest statement for
4 this meeting of October 3rd, 2003. The following
5 announcement addresses conflict of interest issues
6 associated with this meeting and is made part of the
7 record to preclude even the appearance of an
8 impropriety. To determine if any conflict existed,
9 the Agency reviewed the submitted data for this
10 meeting and all financial interest reported by the
11 committee participants. The conflict of interest
12 statutes prohibit special government employees from
13 participating in matters that could effect their or
14 their employer's financial interest.

15 The Agency has determined, however, that
16 the participation of certain members and consultants,
17 the need for whose services outweigh the potential
18 conflict of interest involved is in the best interest
19 of the government. Therefore, a waiver has been
20 granted for Dr. Oliver Schein for his interest in
21 firms that could potentially be effected by the
22 panel's recommendations. The waiver which allows him

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1 to participate fully in today's deliberations involves
2 a pending consulting relationship on a competitor's
3 unrelated product for which he has not received any
4 compensation and also consulting with a competitor on
5 unrelated matters for which he receives between
6 \$10,001.00 and \$50,000.00 yearly.

7 Dr. James McCulley has been granted a
8 limited waiver which allows him to participate in the
9 review and discussion but excludes him from voting on
10 the application. Dr. McCulley's waiver involves three
11 consulting arrangements with competing firms. For
12 these consulting services he received greater than
13 \$50,000.00 within the past year. Copies of these
14 waivers may be obtained from the Agency's Freedom of
15 Information Office, Room 12A-15 of the Park Loan
16 Building.

17 We would like to note for the record that
18 the Agency took into consideration other matters
19 regarding Drs. Bradley, Schein and Coleman, Michael
20 Grimmatt, Allen Ho and Jayne Weiss. Each of these
21 panelists reported past or current interest involving
22 firms at issue but in matters that are not related to

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1 today's agenda. The Agency has determined, therefore,
2 that the panelists may participate fully in the
3 deliberations with the exception of Dr. McCulley, as
4 noted previously.

5 We would also like to note that the Acting
6 Industry Representative for this meeting, Mr. Michael
7 Crompton, reported that his employer has numerous
8 business relationships with firms at issue. In the
9 event that the discussions involve any other products
10 or firms not already on the agenda for which an FDA
11 participant has a financial interest, the participant
12 should excuse him or herself from such involvement and
13 the exclusion will be noted for the record.

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

20 I'd like to read not at this time the
21 appointment to temporary voting status for this
22 meeting. Pursuant to the authority granted under the

1 Medical Devices Advisory Committee Charter dated
2 October 27th, 1990, and as amended August 18th, 1999,
3 I appoint the following individuals as voting members
4 of the Ophthalmic Devices Panel for this meeting on
5 October 3rd, 2003. Drs. William Mathers, Karen
6 Bandeen-Roche, Joel Sugar, Marian Macsai-Kaplan and
7 Oliver Schein. For the record, these individuals are
8 special government employees and consultants to this
9 panel or other panels under the Medical Devices
10 Advisory Committee.

11 They have undergone the customary conflict
12 of interest review and have reviewed the materials to
13 be considered at this meeting. Signed, David W.
14 Feigal, Jr. MD, MPH, Director of the Center for
15 Devices and Radiological Health dated September 26th.
16 Thank you. Dr. Weiss.

17 DR. WEISS: Thank you, Sally. We will now
18 begin the open public hearing. Captain Steven
19 Schallhorn -- I'm sorry, I'm just going to have him
20 approach the podium and then I have a statement. But,
21 I'm sorry, you have a presentation to make to Dr.
22 Matoba. I apologize.

1 DR. ROSENTHAL: I do thank you very much.

2 DR. WEISS: That's very important.

3 DR. ROSENTHAL: I will come over and stand
4 next to her.

5 MS. THORNTON: Give him a microphone.
6 This is important.

7 DR. ROSENTHAL: Hi. I get two kisses this
8 time. I'd like to give this presentation to Alice
9 Matoba and read the Associate Commissioner for
10 External Relations' comments. "Dear Dr. Matoba, I
11 would like to express my deepest appreciation for your
12 efforts and guidance during your term member -- your
13 term as a member of the Ophthalmic Devices Panel of
14 the Medical Devices Advisory Committee. The success
15 of this committee's work reinforces our conviction
16 that responsible regulation of consumer products
17 depends greatly on the experience, knowledge and
18 various backgrounds and viewpoints that are
19 represented on the committee.

20 In recognition of your distinguished
21 service to the Food and Drug Administration, I am
22 pleased to present you with the enclosed plaque". And

1 I am pleased to express my thanks. Alice and I go
2 back a long time.

3 (Applause)

4 DR. MATOBA: Well, thank you, Dr.
5 Rosenthal. It was a great honor for me to be asked to
6 serve as a member of the FDA Ophthalmic Devices Panel
7 and it's been such a great pleasure for me to work
8 with the excellent FDA staff and fellow panel members
9 and with you and especially with Sally Thornton, who
10 has done such a great job.

11 I have been so impressed with the
12 thoroughness and the very high standard of scrutiny
13 that you give to all of the protocols that we have
14 seen and I look forward to continuing to work with you
15 as a consultant in the future. Thank you.

16 DR. WEISS: Thank you, Alice. Thank you,
17 Dr. Rosenthal. We will now begin the Open Public
18 Hearing but first, I wanted to read a statement that
19 was requested by the FDA. "Both the Food and Drug
20 Administration and the public believe in a transparent
21 process for information gathering and decision making.
22 To insure such transparency of the open public hearing

1 session of the Advisory Committee, FDA believes that
2 it is important to understand the context of an
3 individual's presentation. For this reason, FDA
4 encourages you, the open public hearing speaker, at
5 the beginning of your written or oral statement, to
6 advise the committee of any financial relationship
7 that you may have with the sponsor, its product and if
8 known, its direct competitors.

9 For example, this financial information
10 may include the sponsor's payment of your travel,
11 lodging or other expenses in connection with your
12 attendance at the meeting. Likewise, FDA encourages
13 you at the beginning of your statement to advise the
14 committee if you do not have such financial
15 relationships. If you choose not to address this
16 issue of financial relationships at the beginning of
17 your statement, it will not preclude you from
18 speaking.

19 Dr. Schallhorn, we have your presentation,
20 we have up to a half hour for the open public hearing,
21 but you have 10 minutes at this point.

22 DR. SCHALLHORN: Well, good morning, and

1 thank you for allowing me to address the panel. My
2 name is Steve Schallhorn. I'm an ophthalmologist, the
3 Director of Cornea and Refractive Surgery at the Navy
4 Medical Center, San Diego. I have no financial
5 interest in STAAR. I'm not a paid consultant. I've
6 self-funded my travel to come here to address the
7 panel. I am a clinical investigator in the Toric ICL
8 Study, which is ongoing but treatments at our center
9 have not begun.

10 I'd like to also add that I'm an active
11 duty U.S. Navy Ophthalmologist but the views that I
12 express are not necessarily those of the U.S. Navy.

13 The reason I'm here is just to address an
14 important issue, I believe and that is that we need
15 options. We need surgical options, surgical options
16 beyond what we can do with keratorefractive surgery in
17 particular, excimer laser ablative procedures,
18 especially to correct high myopia. There are many
19 issues here and they deal with issues such as thin
20 corneas. There are patients who are not good
21 candidates for refractive surgery because of high
22 refractive errors.

1 Patients with high refractive errors may
2 not be good candidates anyway because current
3 technology induces a number of aberrations on the
4 cornea which can result in visual symptoms. And there
5 are patients or subject that we want to treat that
6 have critical visual demands, especially those again
7 with high refractive error.

8 Now, my area of expertise and what we've
9 studied to a great extent, deals with the quality of
10 vision after refractive surgery and that's really what
11 I'd like to spend the rest of the time talking about.
12 The -- what I'd like to talk about is a study that
13 we've conducted looking at a 105 consecutive LASIK
14 subjects that we had visual acuities measurement on,
15 questionnaires and a special test, a night-driving
16 simulator. I'll talk more about that.

17 This was LASIK performed with multiple
18 laser platforms with a six and a half millimeter
19 optical zone size with a transition zone, so it's the
20 latest technology for high myopia. This was also
21 conventional and not customer wavefront-guided. The
22 average preop refraction was relatively high, it was

1 minus six, a little over minus six diopters and it
2 ranged up to minus 11. At six months the results were
3 good and the uncorrected visual acuity results were
4 satisfactory with about three-quarters of the patients
5 achieving 20/20 uncorrected.

6 The night-driving simulator that we used
7 was a derivative of the simulator that Dr. Ginsberg
8 developed that I believe was required in some earlier
9 investigational studies conducted for intraocular
10 lenses. This test, and it's shown here, you can see
11 the -- it doesn't show up very well, but on the right
12 side, it's looking over the shoulder of a subject in
13 best corrected trial frames right here, looking at a
14 rural night driving scene at 55 mile per hour. It's
15 done in best corrected vision. Each eye is tested
16 independently. There were numerous conditions at that
17 the subject were tested on; that was business signs,
18 traffic signs, pedestrian hazards, et cetera.

19 Six thresholds were made for each one of
20 those conditions for both detection and identifying
21 what that was and it was conducted with and without a
22 glare source simulating driving which led to 144

1 measurements that were made, threshold measurements,
2 per patient and so in these 105 subjects that we
3 tested each eye independently, with this unique test,
4 the data represents thousands and thousands of man-
5 hours because it's extremely labor intensive. They're
6 very, very specialized tests, but nonetheless, it's a
7 performance-based task and that's what I'm going to
8 start with.

9 It is a performance-based task, whereas,
10 other tests, I should say of visual acuity such as
11 contrast sensitivity, you can ask yourself, I
12 certainly pondered this, you know, what does it mean
13 if somebody has a subtle loss of contrast? What does
14 that really mean and that's a very good question?
15 What does that really mean and we're trying to get an
16 answer to that, what does that really mean, but a
17 performance based task built in has some of those
18 answers addressed. This is a task that we are now
19 looking at.

20 We look at that. Under all conditions, in
21 this population of 105 subjects, we find a decrement
22 in night driving performance. How much of a

1 decrement? A little bit. This is the data shown
2 another way and this shows the seconds improvement or
3 the seconds decreased in the detection or
4 identification distance, preop to post-op, so it's a
5 paired analysis and zero represents no change post-op
6 compared to preop and you can see most patients had no
7 change. But the trend and the significant -- and it
8 is significant that there was a loss. About 40
9 percent of patients had one second or longer increase
10 in their detection distance.

11 Now, you could ask also, what does one
12 second mean? Is that significant? We've worked with
13 the National Traffic Safety Administration on the
14 meaning of this and they've conducted studies which
15 have shown that one second is a significant decrement
16 in night driving performance at 55 miles per hour
17 under similar but different circumstances. So it's a
18 -- we're seeing a significant loss in a significant
19 portion of patients treated with LASIK for relatively
20 high levels of myopia.

21 Now, let's look at the vision. This is
22 best corrected and five percent contrast acuity shown

1 on the same chart. In orange, it's best corrected and
2 this is lines gained or lost and you can see most
3 patients had no change but the curve has shifted to
4 the right meaning more patients had improvement than
5 a decrement, consistent with what we see and that's,
6 perhaps, partly due to reduction in minification from
7 the act of putting that correction on the cornea.

8 In contrast to what we see with high
9 contrast acuity, we see a shift to the left or worse
10 with five percent contrast acuity, five percent low
11 contrast acuity. It's an ETDRS eye chart, that five
12 percent level and it's backlit. We see a loss, in
13 fact, 25 percent of patients having measurable loss of
14 contrast acuity with this. How about the
15 symptomatology, most patients have no change in their
16 symptomatology, preop to post-op. However, the curve
17 is shifted slighted toward worse. Again, this is a
18 paired analysis. We're looking at all patients and
19 the difference between post-op and preop. It's
20 slightly shifted worse, meaning patients have
21 symptoms. In fact, a subset of patients can have
22 relatively significant symptoms after the surgery.

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1 Now, we tried to find out, okay, what are
2 the factors that now are related to their driving
3 performance decrement, what are those factors and
4 we've done correlation analysis. And we find
5 surprisingly that pupil size placed no factor
6 whatsoever and I'll talk more about the briefly.
7 Pupil size placed no factor in their night driving
8 performance. Where we see a significant decrement
9 pupil size has no effect. One of the strongest
10 effects we see, though, is the level of preop myopia.
11 The higher level of preop myopia, the worse the night
12 driving symptoms. I'll talk, again, more about that.

13 We also get correlations with
14 symptomatology in night driving performance. We get
15 correlations with the contrast. People who have worse
16 contrast, don't do as well in night driving. That all
17 makes sense. Here's, just quickly, shows the low-
18 light pupil diameter and you can see we had patients
19 that were eight millimeters or larger. We had a wide
20 range of pupils. We did not exclude patients who had
21 large pupils in this study. Just to repeat, we did
22 not exclude patients who had large pupils from the

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1 study. We had a broad distribution of pupil size. We
2 found no correlation with pupil size.

3 And all of the analysis that we've done,
4 other types of analysis with many, many other data
5 sets have shown no correlation with pupil size.
6 However, we do find a significant correlation again,
7 as I mentioned, with preop myopia. Patients who have
8 high levels of preop myopia had a significant decrease
9 in the night-driving performance. You can see on a
10 scatter plot of all the data that there is significant
11 spread. However, there is a significant relationship
12 also.

13 Now, what are the causes of this, what are
14 the causes of these problems after LASIK and the
15 answer is, I think, has to do with higher order
16 aberrations, the induction of higher order
17 aberrations. This is looking at preop, a distribution
18 of the higher order RMS preop and looking at it post-
19 op in yellow and we see a significant increase in the
20 higher order aberrations.

21 We do correlation analysis with those
22 higher order aberrations and we find that the level of

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1 preop myopia is significantly correlated to induced or
2 an increase in spherical aberration. And again, a lot
3 of scatter, but a significant relationship. Likewise,
4 we find that increase in higher order aberrations,
5 higher order RMS, change in higher order RMS
6 vertically versus change in five-percent contrast
7 horizontally that there also a significant
8 relationship. Patients who have increase in higher
9 order aberrations have an increase or a decrease in
10 their contrast acuity.

11 Anyway, in conclusion, conventional LASIK
12 works well. Most patients have no symptoms, but in
13 some patients, it can induce visual symptoms, it can
14 reduce low contrast acuity, it can increase higher
15 order aberrations and it can decrease night driving
16 visual performance. Preop myopia is the strongest
17 risk factor. Patients who are especially above six
18 diopters have the greatest risk and, of course, that's
19 also the range where improved algorithms, improved
20 ways to do LASIK, such as wavefront-guided surgery, is
21 not yet -- is not available.

22 And lastly, we need these kind of surgical

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1 options. Surgical options are needed especially to
2 correct higher orders of myopia. Thank you.

3 DR. WEISS: Thank you, Dr. Schallhorn.

4 (Applause)

5 DR. WEISS: We don't usually have
6 questions at this point, but if anyone had any
7 pressing questions for Dr. Schallhorn, we could limit
8 them to a few, otherwise, we'll -- Dr. Bradley does,
9 Dr. Schallhorn.

10 DR. BRADLEY: Thanks for the presentation,
11 Dr. Schallhorn. One question, you made an emphatic
12 statement that pupil size was not critical. You then
13 inferred from your data that these driving problems
14 were related to higher order aberrations. Well, the
15 one thing we know for use is that as pupil size gets
16 bigger, aberrations get worse. So how can there be a
17 correlation with higher order aberrations but not with
18 pupil size?

19 DR. SCHALLHORN: Well, aberrations can
20 increase as the pupil size increases. But its effect
21 on visual performance is what I'm saying we don't see
22 that effect on visual performance. For instance,

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1 there may be -- I think there are things we really
2 don't understand about the visual system and this
3 comes to the heart of several of them. You can have
4 a very aberrated eye that might have aberrations at
5 seven or eight millimeters but it may not effect
6 visual performance. You can measure it on an
7 aberrometer, but if it doesn't effect visual
8 performance, I'm not sure.

9 You know, I think the central four, five,
10 six maybe larger than that, millimeters, of the visual
11 system is critical for high quality vision but it may
12 not be that the eye has to be that perfect beyond that
13 range, even though we can measure aberrations in that
14 range.

15 DR. WEISS: Thank you very much. We are
16 going to move onto the open committee session with the
17 Division update by Dr. Rosenthal, followed by a Branch
18 update by Donna Lochner.

19 DR. ROSENTHAL: Thank you, Dr. Weiss.
20 This year we are pleased to announce the addition of
21 several members to the staff of our Division and I'd
22 like to introduce them to you. There are actually two

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1 from the Ear, Nose and Throat Branch but I will not
2 introduce them. They're not here and probably will
3 not be playing much of a role, though I will comment
4 on them at the end on their -- who they are.

5 First, I'd like to introduce Lori Austin-
6 Hanberry, who has joined our Division in the position
7 of Project Manager. Amongst her duties will be
8 insuring that the Division meets MDUFA (ph) product
9 review goals. She's a Lieutenant Commander in the
10 Public Health Service, has over 14 years experience as
11 a registered nurse with clinical, instructional and
12 management background. Prior to joining FDA she
13 managed various clinical and administrative operations
14 for the Montgomery County Department of Health and
15 Human Services, most recently managing the Childhood
16 Lead Poisoning and Prevention Program.

17 She was also a Captain in the Air Force
18 Reserves for 11 years. She obtained her nursing
19 degree from Howard University and her Masters Degree
20 in Health Care Administration from Central Michigan
21 University. Lori?

22 Dr. Joseph Blustein is a shared hire with

1 the Office of Surveillance and Biometrics and will be
2 working on post-market issues relating to ophthalmic
3 and ENT devices. He is a Board certified
4 ophthalmologist and former Medical Director of the
5 Wisconsin Peer Review Organization. He has two
6 Masters degrees, one in epidemiology and one in food
7 science. He serves on the Wisconsin Public Health
8 Advisory Committee and we welcome Dr. Blustein.

9 Clay Buttemere went to Virginia Tech to
10 pursue his engineering studies. In 2000 he received
11 his BS in engineering science and mechanic from
12 Virginia Tech. He and his wife, after living in
13 Macedonia, moved to Nashville, Tennessee where he
14 enrolled in graduate studies in the Biomedical
15 Engineering Department at Vanderbilt University. His
16 research in the biomedical optics lab at Vanderbilt
17 involved using optical spectroscopy to assess tissue
18 thermal damage in vivo. In May of 2003, he received
19 an MS degree in Biomedical Engineering from Vanderbilt
20 and in August of this year he joined the FDA as a
21 Biomedical Engineer.

22 Brad Cunningham is also a Biomedical

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1 Engineer, who was hired to work in Donna Lochner's
2 Intraocular and Corneal Implants Branch. He received
3 his undergraduate degree from the University of
4 Maryland in Bioengineering focusing on biomedical
5 instrumentation. After graduation, he is employed
6 full time at Walter Reed Army Institute of Research in
7 the Department of Neuropharmacology in the Division of
8 Neuroscience. Whilst there, he co-authored three
9 papers, two recently published articles focusing on
10 studying the therapeutic intervention window following
11 transient cerebral ischemia and the delayed gene
12 response and he's also in the Public Health Service as
13 you can tell from his uniform.

14 I'd like to announce that the Office of
15 Science and Technology has brought Dr. Ethan Cohen to
16 work as a staff fellow in the Electrophysiology Branch
17 of the Division of Physical Sciences. This is also a
18 shared hire with OST. He will be working in our
19 Division as well. Dr. Cohen's area of expertise is
20 electrophysiology of the retina and Dr. Saviola
21 usurped me. His position is a shared high with the
22 Office of Device Evaluation.

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1 Dr. Cohn comes to CDRH from Harvard
2 University where he was a visiting professor in the
3 Department of Molecular and Cell Biology. Prior to
4 working at Harvard, Ethan was an assistant professor
5 in the Department of Ophthalmology and Visual Sciences
6 at Yale Medical School. His PhD is in anatomy from
7 the University of Pennsylvania Medical School. As an
8 OST staff fellow, he will continue to research
9 synaptic interactions of retinal cells. His review
10 work with ODE will be in the area of retinal
11 prosthetic devices that are reviewed in the
12 Vitreoretinal and Extraocular Devices Branch of DOED.
13 Dr. Cohen.

14 And the final two are from ENT. The first
15 is Dr. Nandkumar, who is an electrical engineer with
16 an MS in EE from Tulane University receiving his PhD
17 from Duke in Electrical Engineering. He is an
18 authority on acoustical issues and will be working in
19 the ENT Branch and the final individual is Dr. Antonio
20 Periera, who is a Board certified otolaryngologist,
21 head and neck surgeon who was trained at the
22 University of Puerto Rico and subsequently came to

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1 work in private practice in Washington, D.C.

2 He has been in the Center for Biologics
3 since 1995 and where he had assisted in formulating
4 regulations for the human tissue program and we
5 pinched him from them and I must say we're delighted
6 to have him join our staff, although there may not --
7 they probably will not be working on ophthalmic
8 issues, they might be if we have issues that relate to
9 their expertise.

10 So we welcome all seven new people and I
11 hope you will all get a chance to work with them and
12 enjoy their company. Thank you.

13 DR. WEISS: Thank you. Donna?

14 MS. LOCHNER: In the spirit of keeping the
15 panel apprised of PMAs that have come before the panel
16 previously, I'd like to discuss two such PMAs. First,
17 P010059 is a PMA for the Morcher endocapsular tension
18 ring used for capsular bag stabilization in patients
19 with pseudo exfoliation syndrome or other situations
20 of compromised zonulas.

21 This PMA was reviewed by the panel in
22 January of 2002. The panel recommended that the PMA

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1 was approvable with requests for essentially a
2 complete reanalysis of the clinical data to resolve
3 discrepancies in the PMA and to clarify information
4 that was presented at the panel meeting. We are in
5 the final stages of review and we expect a decision in
6 the near future.

7 The second PMA is P030002 for the C&C
8 Vision CrystalLens Accommodating Intraocular Lens.
9 This PMA was reviewed by the panel in May of 2003.
10 The panel recommended that the PMA was approvable with
11 requests that the patient satisfaction data be
12 stratified by pupil size and that certain labeling
13 revisions be made. The panel recommended that the
14 lens provides accommodative amplitude of about one
15 diopter. Again, we are in the final stages of review
16 and expect a decision in the near future. Thank you.

17 DR. WEISS: Thank you, Donna. I will ask
18 the sponsor to come to the podium. We are going to
19 begin the presentation of PMA P030016. The sponsor
20 has one hour for their presentation. I would request
21 that each presenter speak into the microphone,
22 initially identify yourself and your relationship with

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1 the sponsor and any potential financial conflicts.

2 DR. LAMIELLE: Good morning. My name is
3 Helene Lamielle and I'm Chief Scientific Officer for
4 STAAR Surgical. We are pleased to present you today
5 PMA P030016 for the Collamer Implantable Contact Lens
6 for the correction of myopia. Presenting on behalf of
7 STAAR Surgical today will be Dr. Steven Slade, from
8 Houston, Texas, Dr. John Vukich, a medical monitor
9 from Madison, Wisconsin and Dr. Henry Edelhauser,
10 Director of Ophthalmic Research at Emory University and
11 Director of Specular Microscopy Reading Center.

12 Dr. Vukich has a financial interest in
13 STAAR Surgical while Dr. Slade and Edelhauser are paid
14 consultants with no financial interest other than
15 compensation for their time. Dr. Donald Sanders will
16 participate in the discussions that follow our
17 presentation. Dr. Sanders has a financial interest in
18 STAAR Surgical.

19 The STAAR Myopic Implantable Contact Lens
20 is the subject of today's panel meeting, is indicated
21 for the correction of moderate to high myopia between
22 minus three to minus 20 diopters and is intended for

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1 placement behind the iris in the posterior chamber of
2 the phakic eye. The design of the ICL is very similar
3 to that of standard plate haptic intraocular lenses
4 used for cataract surgery. However, the ICL has been
5 designed with forward vault to minimize contact with
6 the central anterior capsule of the crystalline lens.
7 The lens material is a hydrophilic biocompatible
8 polymer known as Collamer and has a history of safe
9 use in approved standard posterior chamber intraocular
10 lenses.

11 Here is a photograph of the ICL in the
12 vault of the crystalline lens. The footplates are
13 approximately 100 microns thick and are intended to
14 rest in the sulcus. At this time, I would like to
15 introduce Dr. Steven Slade, who will present the
16 surgical procedure, study method for the PMA clinical
17 trial and effectiveness outcome.

18 DR. SLADE: Okay, thank you, Helene. Good
19 morning. My name is Steven Slade and I certainly
20 appreciate the opportunity to present for you today.
21 I'd like to begin my presentation by describing the
22 procedure used to implant the STAAR ICL. The ICL is

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1 shipped to the surgeon in a sterile glass vial and
2 hydrated in saline solution. The lens is removed from
3 the vial with forceps. The lens is then loaded by the
4 surgeon into a sterile disposal injector cartridge for
5 insertion into the eye and this injection system is
6 just like the ones we commonly use for small incision
7 cataract surgery.

8 The injector is specifically designed to
9 minimize surgical manipulation associated with the ICL
10 insertion. Iridotomies are performed up to two weeks
11 before the ICL surgery. The pupil is dilated and the
12 entire surgery is performed under topical anesthesia.
13 Viscoelastic is placed in the anterior chamber. The
14 lens is injected through a spornia (ph) cataract-style
15 incision.

16 Now, the surgery is completed then by
17 positioning the lens haptics beneath the iris and
18 rinsing out the Viscoelastic. The lens centers
19 extremely well and no sutures were necessary in
20 virtually all cases. The STAAR ICL is specifically
21 designed to vault over the anterior capsule of the
22 human crystalline lens. This vault should be

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1 approximately 500 microns or one corneal thickness.
2 This shine through (ph) photograph demonstrates an
3 average vault with the STAAR ICL.

4 The clinical study of the STAAR ICL
5 described in this PMA was a prospective multi-center
6 clinical trial designed to evaluate the safety and
7 effectiveness of this lens for the correction of
8 moderate to high myopia. Patients with myopia of
9 minus three to minus 20 were enrolled and followed for
10 three years. The study was originally planned for a
11 two-year follow-up under the IDE which was approved in
12 1995.

13 During the study, follow up was extended
14 to three years at the FDA's recommendation to be
15 consistent with more recent guidance for studies of
16 phakic refractive intraocular lenses. Our patients
17 were required to be between 21 and 45 years of age and
18 of note, their best corrected vision pre-optimally
19 could be as poor as 2100, and they were allowed to
20 enroll with as much as two and a half diopters of
21 refractive cylinder, since moderate to high myopia is
22 associated with lower levels of best corrected visual

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1 acuity, and higher amounts of cylinder. Our effective
2 parameters included a decrease in refractive myopia,
3 improvement in uncorrected visual acuity,
4 predictability of the refractive outcomes, refractive
5 stability and patient satisfaction.

6 Safety parameters included a preservation
7 of best corrected visual acuity. Slit lamp findings,
8 intraocular pressure, contrast sensitivity with and
9 without glare, reports of complications in adverse
10 events. Specular microscopy was also performed and
11 we'll present the results in detail of those studies.
12 Accountability; 539 eyes of 305 patients were
13 implanted with the ICL. Thirteen eyes of 11 subjects
14 did not meet the entry criteria and were excluded from
15 the safety and effectiveness cohort.

16 This accountability was well within FDA
17 guidance of no more than 10 percent loss per year of
18 follow up. Even though the study was originally
19 planned for only two years of follow up,
20 accountability at three years was 77.2 percent,
21 exceeding the target of 70 percent identified in the
22 FDA's draft guidance for refractive implants. Again,

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1 even though the FDA guidance requires a minimum of 80
2 percent accountability at two years, we had follow up
3 on 91 percent of our cohort and at three years, we
4 were well above the minimum follow up of 70 percent of
5 patients.

6 The demographics of the study population
7 were fairly unremarkable but it is worth noting that
8 the average mean myopia preoperatively in this
9 population was over 10 diopters, minus 10.1 diopters.
10 Now, I'd like to show you uncorrected visual acuity
11 for the entire study cohort and then uncorrected
12 visual acuity for the eyes that had the potential
13 preoperatively to achieve 20/20 uncorrected vision as
14 well as then the eyes that had the potential and were
15 actually able to be targeted to emmetropia or 20/20.

16 Because we enroll patients with up to 20
17 diopters of myopia, not all eyes had the potential for
18 20/20 nor were all eyes able to be targeted to
19 emmetropia. In part, this was the result of limits on
20 the range of lens powers available during this study.
21 If we look at the entire cohort of study patients, the
22 uncorrected visual acuity over time 20/40 or better,

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1 excellent uncorrected distance visual was achieved
2 rapidly, 80 percent at one week, 20/40 or better and
3 had excellent stability, 81 percent 20/40 or better
4 uncorrected at the three-year visit.

5 Again, looking at the entire study cohort,
6 but at the 20/20 level, we see again, a rapid
7 improvement in uncorrected acuity and excellent
8 stability. It should be noted that the total cohort
9 of eyes, this slide, includes those eyes that were not
10 able to be targeted for emmetropia, eyes with
11 preoperative best spectacle corrected visual acuity
12 worse than 20/20 and eyes that had up two and a half
13 diopters of refractive cylinder.

14 Here's the breakout for uncorrected visual
15 acuity for the entire study cohort at three years
16 showing the 20/20, 20/25, 20/30 and 20/40 levels.
17 Now, if you take that same format, I'd like to show
18 you the results for eyes that had the potential for
19 20/20 uncorrected vision. In this group, 89 percent,
20 of 250, 89 percent reached 20/40 or better at the
21 three-year visit and 52 percent were 20/20 or better,
22 the eyes that had the potential preoperatively to

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1 reach 20/20, and the results get even better if we
2 look at the patients who had both the potential to
3 achieve 20/20 and were able to be targeted to
4 emmetropia. In this population, good visual
5 potential, 59 percent were 20/20 or better at the
6 three-year visit and 95 percent were 20/40 or better
7 uncorrected at their three-year visit. If we take the
8 population and stratify it by preoperative myopia as
9 in this slide, with less than 7, 7 to 10, 10 to 15 and
10 over 15, it's apparent that the uncorrected visual
11 acuity of 20/40 or better and of 20/20 or better was
12 achieved by a lower portion of the eyes with
13 preoperative myopia greater than minus 15.

14 It's not unexpected given that the
15 majority of these eyes could not be targeted for
16 emmetropia and the lens powers were not available to
17 allow for full correction of all eyes in this group.
18 Further, in this group of the highest myopes, only
19 four eyes had best corrected visual acuity of 20/20 or
20 better preoperatively. In fact, if we look at the
21 patients again stratified by myopia, who had the
22 potential for 20/20 and were targets of emmetropia, we

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1 see excellent results at both the 20/40 and the 20/20
2 levels of uncorrected vision.

3 But indeed, none of the patients who were
4 in the over 15 group actually even had the potential
5 for 20/20 at the same time they were able to be
6 targeted to emmetropia. We'll have more to say about
7 this group of higher myopes, over 15, later in the
8 presentation since it certainly is a unique
9 population.

10 From a patient's perspective, this
11 efficacy ratio slide comparing the post-operative
12 uncorrected visual acuity to the preoperative best
13 corrected visual acuity may be the most important data
14 in this part of our presentation, since this is what
15 patients are seeking, uncorrected vision, better than
16 or equal to what they were able to see before surgery
17 with their best spectacle correction. The efficacy
18 ratio for the ICL was excellent with upwards of 60
19 percent of patients seeing as well or better after
20 surgery with nothing, no correction, than they were
21 able to see before surgery with their very best
22 spectacle correction.

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1 We examined the standard metrics of
2 predictability of refractive outcome as well as
3 refractive stability. As indicated on this slide, our
4 achieved levels of plus or minus a half and plus or
5 minus one attempted versus achieved, were excellent
6 and did exceed FDA targets for both phakic IOLs and
7 refractive lasers were greater than minus seven
8 diopters of myopia. Accuracy of the attempted
9 refractive change was excellent in eyes of pre-
10 operative myopia looking at the cohort stratified by
11 myopia up to minus 15 and then did, indeed, decrease
12 for the myopes with a baseline myopia greater than 15
13 as you can see in this slide, again, three years
14 looked at the entire cohort stratified by myopia.

15 This slide pretty much speaks for itself.
16 This is our stability slide. The achieved refractive
17 change was again, both rapid, one week, and
18 sustainable throughout the follow up minus a half,
19 minus a half at 36 months. These outcomes do exceed
20 FDA guidance for stability of manifest spherical
21 equivalent refraction.

22 A patient survey was administered to all

1 study subjects and I will share the three-year results
2 of that survey with you. Ninety-nine percent of our
3 patients reported very extremely or moderately
4 satisfied. When asked to rate their quality of
5 vision, 77 percent reported very good or excellent
6 quality of vision as compared to 55 percent of
7 patients before the surgery. Indeed, 97 percent of
8 the study patients expressed a willingness to have the
9 ICL surgery again. The unwilling included eyes with
10 refractive errors, hyperopia (ph), myopia, vomiting
11 right after surgery, and one patient who questioned
12 why repeat the surgery when they had already had the
13 surgery and were doing fine.

14 To summarize, our uncorrected distance
15 visual acuity at three years all eyes in the yellow
16 was excellent. Eighty-one percent of the entire
17 cohort achieved 20/40 or better and 95 percent of the
18 entire cohort stratified now for those people that had
19 the potential to see 20/20 and were able to be
20 targeted for 20/20, 95 -- that group, 95 percent of
21 those patients achieved 20/40 or better uncorrected
22 visual acuity.

1 Predictability of refractive outcome was
2 also excellent, exceeding FDA targets with a
3 significantly -- a very small amount of patients
4 winding up over-corrected or under-corrected,
5 particularly in view of the very broad range of high
6 to moderate myopia treated and this does, again,
7 exceed FDA targets.

8 And now I would like to introduce Dr. John
9 Vukich, who was the medical monitor for the ICL
10 clinical trial. Dr. Vukich will present safety
11 outcomes and he'll be followed by Dr. Henry Edelhauser
12 who will discuss the specular microscopy outcomes for
13 the ICL study. Thank you.

14 DR. VUKICH: Good morning. My name is Dr.
15 John Vukich and I am the medical monitor of the STAAR
16 Surgical Implantable Contact Lens Clinical Trials. I
17 have a financial interest in STARR Surgical. I will
18 be presenting the safety outcomes for the study
19 cohort.

20 Key safety parameters that were analyzed
21 and will be presented include preservation of best
22 spectacle corrected acuity, complications and adverse

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1 events, lens opacities, inflammation, patient
2 symptoms, contrast sensitivity and endothelial cell
3 analysis. There was a rapid and sustained return of
4 best spectacle corrected visual acuity in the study
5 population beginning at one week and continuing
6 through every follow up interval through the three-
7 year period. At every follow up visit the proportion
8 of eyes with 20/40 best corrected acuity was improved
9 over the baseline preoperative level of 97 percent.
10 When we break out the best spectacle corrected acuity
11 at three years, the improvement experienced by the
12 study population is even more notable particularly
13 with regard to the improvement in spectacle correction
14 of 20/20 and 20/25.

15 Thus, these patients have the potential to
16 benefit not only with regards to uncorrected acuity,
17 but also in terms of best spectacle corrected acuity.
18 This study population is quite different from other
19 populations that have undergone refractive surgery
20 evaluations in that only 69 percent of the preop
21 cohort could be corrected to 20/20 or better. We
22 believe this is a unique feature of this cohort and

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1 reflects the high level of myopia and the unique
2 challenges these patients face.

3 When we stratify postoperative best
4 corrected acuity by baseline myopia, at every level of
5 myopia, the ICL cohort experienced an improvement in
6 best corrected acuity at 20/20 or better as compared
7 to baseline. The highest myopes, those with
8 preoperative myopia greater than 15 diopters, also
9 experienced a substantial improvement at the 20/40
10 level. The most dramatic increase was observed in
11 those patients with the highest level of myopia.
12 While we acknowledge the contribution of magnification
13 in this group of very highly myopic patients, the
14 visual results are real and are enjoyed by the
15 patients.

16 When we look at the changes in lines of
17 best spectacle corrected acuity, 49 percent of eyes
18 gained one or more lines of acuity at three years.
19 This contrasts with only eight percent of eyes that
20 lost one or more lines of best corrected acuity.
21 Complications and adverse events are an important
22 aspect of the evaluation of the ICL and we examined

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1 this from several perspectives. Perioperative
2 complications were reported for 17 eyes, the most
3 common of which was removal and reinsertion on the day
4 of surgery.

5 A small number of other perioperative
6 complications was also reported and these included
7 reformation of the anterior chamber, a peripheral
8 iridectomy and repair of iris prolapse. Postoperative
9 complications other than intraocular pressure rises,
10 lens opacities or secondary surgical procedures were
11 reported in five of the 526 eyes in the study cohort
12 for an incidence of less than one percent. Since
13 there were so few of these cases in this category, I
14 think it is useful to describe each of these
15 individually.

16 One eye experienced a macular hemorrhage
17 at one week and this result without sequelae. An
18 asymptomatic subretinal hemorrhage was observed as an
19 incidental finding at the three-month visit and best
20 corrected visual acuity remained unchanged from
21 baseline in this eye. Three retinal detachments were
22 reported during the three years of follow up in this

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1 ICL clinical trial. One eye had a retinal detachment
2 with a macula off. This required repair with silicon
3 oil and a subsequent nuclear pacification was noted
4 with loss of best corrected acuity to count fingers.
5 This patient represents the only case in the study
6 cohort with irreversible loss of acuity to worse than
7 20/40. This patient had 16 diopters of myopia
8 preoperatively.

9 Two other retinal detachments were
10 reported during the course of the clinical trial.
11 Both cases were successfully repaired such that the
12 final best corrected visual acuity remained within one
13 line of the preoperative spectacle correction. Based
14 on published reports, and incidents of retinal
15 detachment of .68 percent per year might have been
16 anticipated and we might have anticipated as many as
17 nine retinal detachments in this study cohort that is
18 following 526 eyes over three years. That fact that
19 we had only three retinal detachments in this study
20 suggests that the ICL had limited or no impact on the
21 incidents of this adverse event.

22 Intraocular pressure rises occurred in 20

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1 eyes or 3.8 percent of the study cohort. The majority
2 of the acture pressure rises occurred during the first
3 one to two days after surgery. Preoperative
4 iridotomies were performed on all study eyes as a
5 routine part of the ICL surgery. Seventeen eyes
6 required additional YAG iridotomy or enlargement of an
7 existing iridotomy for control of intraocular
8 pressure. Irrigation of the anterior chamber for
9 removal of retain viscoelastic was performed in three
10 eyes. Late intraocular pressure rises occurred in
11 five eyes or less than one percent of the cohort.
12 This was defined as a single reading intraocular
13 pressure of 25 millimeters or greater or an increase
14 over baseline of 10 millimeters of mercury at three
15 months or later.

16 In three of these eyes the intraocular
17 pressures are being monitored without intervention and
18 the most recent pressures are shown on this slide.
19 Two eyes are currently being treated with a topical
20 beta blocker. The most recent intraocular pressure
21 for these patients are 20 millimeters of mercury or
22 less. Secondary surgical procedures were performed in

1 three percent of the study cohort. The most common
2 procedure was removal and replacement as a result of
3 sizing issues.

4 Repositioning was performed in four study
5 eyes. One ICL was replaced for a power
6 miscalculation. In the entire study cohort only three
7 eyes underwent ICL removal and cataract extraction
8 representing .6 percent of the entire study
9 population. This summary slide shows all of the
10 secondary ICL surgeries. I'd like to point out that
11 only a single eye lost best corrected acuity and this
12 loss was only one line occurring in one eye that
13 underwent and ICL repositioning. It is particularly
14 noteworthy that those patients who underwent cataract
15 extraction maintained their best spectacle corrected
16 acuity relative to their preoperative level prior to
17 insertion of the ICL.

18 Assessment of the crystalline lens was an
19 area of significant concern and this was monitored
20 carefully throughout the course of the study. Nuclear
21 opacities were observed in five eyes of three
22 patients. In a patient who was previously described,

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1 a nuclear opacification occurred following retinal
2 detachment which was repaired with silicon oil. Both
3 eyes of two patients developed simultaneous bilateral
4 nuclear opacities between two and three years
5 postoperatively and one of these four eyes required
6 cataract extraction. Once again, it should be noted
7 that all of these eyes were very highly myopic ranging
8 from minus 14 to minus 17 diopters.

9 Lens clarity was graded at all patient
10 visits using the LOCS 3 Scale. This scale ranges from
11 zero to 5.9 and under this system a Grade 1 was best
12 described as a trace opacity. Given here is the
13 photographic standard for Grade 1. I'd like you to
14 keep this photograph in mind since over half of the
15 anterior subcapsular opacities we are going to
16 describe were no greater than this clinical standard.
17 In fact only one eye in the study had an anterior
18 subcapsular change at Grade 2 or higher.

19 Anterior subcapsular opacities were
20 observed in 14 eyes of 13 patients. It is important
21 to note that 12 of these 14 cases were asymptomatic
22 and visually insignificant at the most recent follow

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1 up visit. We believe that many of these cases were
2 surgically related and this is supported by the fact
3 that 11 of these cases occurred within the first six
4 months of surgery.

5 Clinically significant anterior
6 subcapsular opacities were observed in only two eyes.
7 These were defined as LOCS score of less than --
8 greater than .5 with a loss of two or more lines of
9 best spectacle corrected acuity or an increase in
10 glare or a opacity requiring ICL removal with cataract
11 extraction. One of these cases was a surgical mishap
12 in which a preservative containing topical miotic was
13 inadvertently injected into the anterior chamber.

14 The second case was an eye in which an
15 opacity was observed six months postoperatively.
16 Cataract surgery was performed and post-cataract best
17 corrected acuity was unchanged from the pre-ICL
18 baseline. To summarize our findings on lens
19 opacities, only three cataract extractions were
20 performed in the study population of 526 eyes.

21 One was related to the inadvertent
22 injection of a topical preserve miotic into the eye.

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1 One was a nuclear cataract and the third case was an
2 anterior subcapsular opacity that did progress to the
3 level of clinical significance. Best corrected visual
4 acuity was unchanged or improved following cataract
5 extraction in all three eyes compared to pre-UCL
6 treatment. Safety may be best summarized in eye -- by
7 examining the eyes with persistent loss of best
8 corrected acuity of two or more lines. There are only
9 five of these eyes and you have seen all of these
10 cases previously in our presentation on safety.

11 Here is the retinal detachment repaired
12 with silicone oil and the eye irrigated intracamerally
13 with preserve miotic agent. Additionally, three of
14 the nuclear opacities had a persistent loss of two or
15 more lines of best corrected acuity. One of these
16 we've just described had cataract extraction. In the
17 entire clinical trial, these are the only eyes that
18 had a persistent loss of two lines or more of best
19 corrected acuity.

20 Next I would like to present our findings
21 related to inflammation. Slit lamp examination was
22 performed in all study eyes at all visits and a laser

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1 cell-flare meter was used to evaluate information in
2 a sub-study of patients. No inflammatory response was
3 observed after the first week postoperatively either
4 clinically or by the more sensitive laser cell-flare
5 meter. Laser flare measurements following ICL
6 implantation were within the normal range for the
7 first post-operative week, and remained normal
8 throughout the course of the entire clinical trial.

9 A subjective questionnaire was
10 administered to all study patients preoperatively and
11 at follow up examinations. Patients were asked to
12 rate each of the symptoms listed on this slide as
13 either absent, mild, moderate, marked or severe. When
14 comparing preoperative responses to those attained at
15 three years, there were no significant changes in
16 symptoms rated as absent or mild.

17 Equally importantly is the fact that there
18 were no significant changes from baseline to three
19 years in symptoms rated as moderate, marked or severe.
20 Contrast sensitivity and glare were evaluated in a
21 sub-group study. Well established techniques were
22 used in our contrast sensitivity testing. After 10

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1 minutes of dark adaptation, measurements were made
2 both with and without a glare source. There was no
3 loss of contrast sensitivity at any spacial frequency
4 when compared to baseline to postoperative results.
5 In fact, at two frequencies there was a significant
6 increase in log units of contrast sensitivity. When
7 contrast sensitivity was repeated in the presence of
8 a glare source, there was a significant improvement at
9 all four spacial frequencies starting at three cycles
10 per degree up to 18 cycles per degree.

11 I would now like to introduce Dr. Henry
12 Edelhauser who will be presenting the Specular
13 Microscopy Substudy.

14 DR. EDELHAUSER: Thank you, John. Good
15 morning. I'm Dr. Henry Edelhauser, Director of
16 ophthalmic research at Emory University. I have no
17 financial interest in STAAR Surgical. I serve as
18 Director of the Specular Microscopy Reading Center for
19 the ICL clinical trial and will be presenting the
20 results of a sub-study conducted by STAAR Surgical to
21 evaluate the effects of the ICL implantation on the
22 corneal endothelium. I would like to emphasize the

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1 importance of the methods used at the Specular
2 Microscopy Reading Center. Images were received from
3 12 investigators at nine clinical sites and a signal
4 masked reader analyzed all the images. The images
5 were then scanned and analyzed with the Konan KSS-300
6 Software. Approximately 1300 images were analyzed in
7 this study and the mean number of cells per image that
8 was counted was 93. This slide shows how the images
9 were handled and that the images were taken with a
10 Konan. They were then sent to us in the reading
11 center as hard copy. We then scanned them. We then
12 resized them and formatted the images. We then
13 calibrated and analyzed, put it in a spreadsheet and
14 then sent the data back for statistical analysis at
15 STARR.

16 I think it's important when we talk about
17 specular microscopy to review what a good image is
18 because not all specular microscope and reading
19 centers and photographers are able to take good images
20 and this is the real challenge in undertaking specular
21 microscopy. One, it's important to have distinct
22 cells as illustrated on the right. In the specular

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1 micrograph one can identify 100 cells and even more in
2 that's essentially what we do at the reading center is
3 to identify as many cells as possible because when you
4 analyze this, it's done by putting a dot in each one
5 of the cells and then the analysis software is the
6 nearest neighbor analysis. So cells in the periphery
7 that don't have a nearest neighbor are not counted.

8 Cells need to be grouped into form in a
9 contiguous area and then after you have dotted all the
10 cells, it's extremely important that the evaluator or
11 the reader check to see that the cells haven't been
12 double-dotted or cells missing because if you miss
13 three cells, you have a significant change in the end
14 of field cell density because what you see from this
15 specular micrograph is multiplied by 10. Precision
16 of the readings is an important factor in the analysis
17 of any endothelium. We have estimated that the
18 precision to be two percent in the ideal situation
19 which was published in our study of LASIK patients.
20 In this particular case we had one single clinical
21 site, photographer and one single reader. When you
22 undertake multi-center study where you have numerous

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1 photographers and then you then send this to a reading
2 center and one single reader, the precision is
3 somewhere between eight to 10 percent.

4 The outcomes of our analysis of the
5 corneal endothelium are shown in this slide and
6 include endothelial cell density, percent
7 hexagonality, or pleomorphism and coefficient of
8 variation or polymegathism. Studies indicate that
9 stress corneas present -- have a percent hexagonality
10 of less than 45 and a coefficient of variation greater
11 than 45.

12 Published studies and studies from my own
13 laboratory have shown that morphology is the best
14 indicator of corneal endothelial stress and
15 instability. I would now like to share with you some
16 examples where endothelial morphology has been
17 demonstrated to be the most sensitive measure of
18 corneal endothelium stability. These examples are
19 pseudophakic bullous, diabetes, and contact lens wear.

20 In this seminal paper, published by Rao
21 and Aquavella in 1984, they studied patients implanted
22 with iris fixated lenses in patients whose corneas

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1 made clear shown in the yellow bars, were compared to
2 patients who ultimately developed corneal edema in the
3 blue bars. Interesting, these authors found no
4 difference between the two groups with regard to
5 percent endothelial cell loss. However, there was a
6 marked difference in coefficient of variation
7 indicating that morphology is a more sensitive
8 indicator for the development of bullous keratopathy.

9 In the second illustration, the corneal
10 endothelium is illustrated in diabetes and this was
11 published from one of our papers in 1984 where we
12 reviewed the endothelium of both Type 1 and Type 2
13 diabetics. In this study we showed there was no
14 significant difference in endothelial cell density but
15 there was a significant difference -- decrease in
16 percent hexagonality and a significant increase in
17 coefficient of variation.

18 The next example that shows the importance
19 of morphology is related to endothelial cell density
20 is provided in a study by McRae and Matsuda, et al,
21 and they compared patients who used contact lenses for
22 more than 20 years and compared to age-match controls.

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1 Again there was no significant difference in
2 endothelial cell density, a significant decrease in
3 hexagonality and a significant increase in the
4 coefficient of variation.

5 The three examples I've shown demonstrate
6 the corneal endothelial morphometric changes are the
7 first indicators of endothelial stress. The percent
8 hexagonality and coefficient of variation are more
9 sensitive indicators of endothelial stability than
10 endothelial cell density.

11 I would now like to review the ICL STAAR
12 PMA data on endothelial morphology. This graph is a
13 scattergram of all pre and post-operative data points.
14 In general, the majority of the points were between
15 2,000 and 3,000 cells per millimeter square with a
16 small number our outlyers. The dark bars in the
17 center of the scattergram illustrate the mean plus or
18 minus 90 percent of the confidence interval. This
19 slide shows a similar scattergram but with data points
20 for a consistent cohort of 37 eyes with specular
21 microscopic data in all visits from preop to four
22 years.

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1 This slide does show that the endothelial
2 cell density remains unchanged from three to four
3 years.

4 DR. GRIMMETT: Do you know the confidence
5 intervals at the last visit?

6 DR. EDELHAUSER: Yes, I have it. It's
7 coming up in the next slide.

8 DR. GRIMMETT: Thank you.

9 DR. EDELHAUSER: The table shows the pair-
10 wide comparison of endothelial cell density at
11 consecutive intervals beginning with the preop to
12 three months a minus .2 was measured and cell loss was
13 observed and from three months to one year a minus .9
14 percent observed. Between three and four years, a
15 plus .1 percent and a narrow confidence limits of 1.4
16 percent to plus 1.6 percent. The percent hexagonality
17 data shows no change over the course of study in this
18 cohort of patients.

19 For comparative purposes, a percent
20 hexagonality of 45 would be an indication of a
21 stressed corneal endothelium. The coefficient of
22 variation data also shows no increase over the course

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1 of study of this cohort. Again, for comparative
2 purposes, a coefficient of variation of 45 would be an
3 indication of a stressed corneal endothelium. In
4 summary, the specular microscopic data show a
5 cumulative or a total mean endothelial cell loss of
6 8.4 percent to 9.7 percent over a course of four-year
7 follow up with stabilization suggested at the four
8 years. It should be noted that there is no apparent
9 mechanism for chronic cell loss due to the ICL. This
10 is supported by the absence of changes in the percent
11 hexagonality and coefficient of variation, which do
12 not indicate chronic endothelial cell stress in this
13 study population. This conclusion is supported by the
14 previous reported data on pseudophakic loss, diabetics
15 and contact lens wear.

16 We don't have a long-term study of
17 endothelium in high myopes in the peer review
18 literature. But we know that extrapolating
19 endothelial cell densities over time is complex. It
20 should be noted that the endothelium is not a
21 homogenous population of cells from central to
22 peripheral and migration of endothelial cells must be

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1 considered in any long term modeling of the
2 endothelial cell density.

3 Recent data published from my laboratory
4 in March of this year in the AJO, addressed the issue
5 of peripheral corneal endothelial cells. In this
6 study we found that if, indeed, you measure the
7 corneal endothelium here and then you go two
8 millimeters off in the paracentral region, there's a
9 five percent increase in the corneal endothelium. And
10 if you go four millimeters off center, there is a 10
11 percent increase in endothelial cell density.

12 Now, let's put this into perspective with
13 this. The cell density within a four millimeter
14 button is roughly 34,740. The paracentral region has
15 a cell density of 119,845. And four millimeters off
16 center in this area where we have a high cell density,
17 the cell density is calculated out to be 264,632 cells
18 per millimeter square. Now, this is not a study that
19 doesn't have backup because it had first been
20 identified by Bert Chimifane (ph) in 1984 and
21 subsequently two papers in the German literature in
22 '89 and '90, all showing an increase in the peripheral

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1 corneal endothelium. I do want to say that in this
2 study we measured the corneal endothelial cells in
3 four different ways; non-contact specular microscopy,
4 contact specular microscopy, alizarin red staining of
5 corneas we received from the eye bank, and also fixed
6 corneas where we developed the nomogram to correlate
7 with the pathologist the number of corneal endothelial
8 cells as measured by the nuclei in high power field
9 correlated to a nomogram of endothelial cell density.

10 The higher the endothelial cell density
11 found in the paracentral and peripheral cornea affords
12 an additional reassurance of safety for the
13 endothelium in the patients implanted with the ICL.
14 In summary, stability appears to be achieved between
15 three years and four years in the ICL population.
16 This data -- these data are consistent with
17 endothelial remodeling and stabilization. The absence
18 of any effect on the percent hexagonality, coefficient
19 of variation support the absence of stress on the
20 corneal endothelium. This would be consistent with an
21 implant placed behind the iris and suggests that the
22 endothelial cell loss observed in the ICL clinical

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1 trial is related to the initial surgical procedure and
2 not a chronic phenomena.

3 Ongoing surveillance of the corneal
4 endothelium will be critical to establishing the
5 continual safety of the ICL and the study sponsor is
6 committed to collecting the additional four-year
7 follow up patients. Patients will also be asked to
8 return for five-year specular microscopic exams and
9 the same rigor and precision will be used to evaluate
10 that corneal endothelium by the reading center. I
11 would now like to turn the podium over to Dr. John
12 Vukich.

13 DR. VUKICH: Once again, I am Dr. John
14 Vukich. A unique group in our clinical trials
15 represented by the patients with more than 15 diopters
16 of myopia. This group deserves special attention
17 since concerns have been expressed by both the FDA and
18 panel reviewers regarding acceptability of study
19 outcomes in this population. I think we all
20 understand the unique challenges represented by this
21 group of extremely myopic patients. These include
22 significant variability in simply determining the end

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1 point of the manifest refraction. Many of these
2 patients have poor visual acuity even with their best
3 spectacle corrected acuity. In spite of this, the
4 mean post-operative spherical equivalent was reduced
5 from minus 17.3 diopters to minus 2.2 diopters with
6 the implantable contact lens for an average correction
7 of 88 percent of the pre-existing myopia. At the time
8 of the ICL clinical trial, lens powers were not
9 available to achieve full correction to emmetropia in
10 all cases. Even with this limitation, 39 percent of
11 eyes with greater than 15 diopters of myopia achieved
12 an uncorrected acuity of 20/40 or better.

13 Substantial improvement was observed in
14 the proportion of eyes with best corrected acuity of
15 20/40 or better. The proportion of eyes with best
16 corrected acuity of 20/20 or better increased from 13
17 percent at baseline to 42 percent at three years. We
18 acknowledge that magnification contributes to the
19 observed improvement in best corrected acuity but
20 continue to believe that this improvement in best
21 corrected vision is an important benefit to the
22 patient.

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1 Any analysis of complications and adverse
2 events in this population of high myopes must be
3 viewed relative to their baseline risk. A body of
4 published literature has established that the risk of
5 spontaneous complications such as retinal detachment
6 and nuclear opacities is significantly increased in
7 high myopes. For example, the risk of detachment of
8 the retina is 26 times higher in myopes above minus 6
9 diopters. A significantly increased risk has also
10 been established for the incidents of nuclear
11 opacities in highly myopic patients. These
12 complications must be viewed in the context of the
13 increased risk of the population. Given the
14 additional risk it should not be surprising that a
15 higher rate of complications was observed in the
16 subset of highly myopic patients.

17 Review of these complications which have
18 already been presented as part of the safety data for
19 the total study population revealed that two retinal
20 detachments and four nuclear opacities were observed
21 in six eyes. Only the eye with complicated detachment
22 requiring silicone oil has had an irreversible loss of

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1 vision. In fact, this is the only eye in the entire
2 clinical trial in this category.

3 With the exception of the eye with retinal
4 detachment requiring silicone oil, all of these
5 patients were satisfied with the outcome of ICL
6 implantation and would be willing to undergo surgery
7 again. We have shown that these patients had a
8 substantial improvement uncorrected visual acuity and
9 over half of these eyes experienced a gain in best
10 corrected acuity. We believe that these are the very
11 patients that stand to gain the most from implantation
12 of an ICL particularly in the absence of alternative
13 devices or surgeries for the correction or reduction
14 of their myopia.

15 In summary, the data presented to you on
16 the outcomes in this PMA serve to establish the safety
17 and effectiveness of the myopic ICL for its intended
18 use in myopia from minus 3 to minus 20 diopters. We
19 believe that the concerns raised by the FDA and panel
20 reviewers can and should be addressed. To this end,
21 we are committed to long-term surveillance of the
22 study population with regard to endothelial cell

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1 analysis. We also believe that a comprehensive
2 training program is an essential part of achieving
3 successful outcomes with the ICL and plan to require
4 formal training and certification for all surgeons who
5 use this device.

6 Finally, we believe that labeling can be
7 developed to adequately communicate the risks as well
8 as the benefits of the ICL and we welcome labeling
9 recommendations from both FDA and panel. This will
10 allow surgeons and patients to make informed decisions
11 on the use of the ICL and the appropriateness of this
12 device for each individual patient. We believe that
13 the data presented to you today and the safeguards we
14 are proposing in terms of long-term patient
15 surveillance, surgeon training and adequate labeling
16 support a panel recommendation for approval of the ICL
17 as an important option in the management of myopia.
18 Thank you and this concludes the formal presentation
19 by the sponsor.

20 DR. WEISS: I'd like to thank the sponsor
21 for their presentation and if they'd remain at the
22 podium, we will begin for questions from the panel to

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1 sponsor on their presentation. Dr. Macsai?

2 DR. MACSAI: My question is directed at
3 Dr. Edelhauser. The slide you showed of the 37
4 patients, the standard cohort of endothelial cells
5 changing, on the next slide you said you would address
6 the coefficient variation confidence intervals and
7 that slide was not for that 37 patient cohort. This
8 is new information and I think that data would help us
9 figure out more information about the endothelial
10 cells.

11 DR. EDELHAUSER: Yes, I'd like to turn
12 this -- this was data that came back to us.

13 DR. WEISS: Please, would you be able to
14 identify yourself each time you speak in the mike for
15 the transcription.

16 DR. EDELHAUSER: I'm Dr. Edelhauser. This
17 data came from Dr. Gray, the statistician from the FDA
18 when he sent his review back to STAAR where he then
19 broke out and calculated this cohort of patients from
20 the start or the pre-op all the way to four years.

21 DR. MACSAI: But what is the -- this is
22 Dr. Macsai.

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1 DR. SANDERS: Dr. Gray did not include
2 that in --

3 DR. WEISS: Please identify yourself.

4 DR. SANDERS: Dr. Sanders. We used the
5 analysis that Dr. Gray provided us on the Internet and
6 it did not include the confidence intervals.

7 DR. MACSAI: Dr. Macsai speaking. But
8 does STAAR have the same patients followed from pre-op
9 all the way through to four years, those 37 patients?
10 Do you have that information, can you provide that
11 information to us?

12 DR. VUKICH: We do have those patients and
13 again, this is an analysis -- I'm sorry, Dr. John
14 Vukich. We do have that analysis available and can
15 provide that to the panel.

16 DR. MACSAI: Thank you.

17 DR. WEISS: Dr. Grimmett?

18 DR. GRIMMETT: Sure, Dr. Michael Grimmett.
19 I have a number of questions as you can well imagine.
20 The first one to Dr. Edelhauser; I really appreciated
21 your review of the endothelial morphology data and I
22 would just like to ask you regarding that data of

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1 endothelial stress, has it ever been stratified (sic)
2 by corneal age, that is do younger corneas have a
3 blunted endothelial morphometric alteration as
4 compared to old corneas with less endothelial cushion
5 or reserve?

6 DR. EDELHAUSER: Dr. Edelhauser. The best
7 data stratification that I can think of to answer the
8 question is the data that we published in '84 on the
9 diabetic corneas. In there we broke it down in terms
10 of decades. And indeed, if you look at the bar graph
11 that is published in that paper, you will find that
12 there is -- as one ages, there is both a progressive
13 decreased in percent hexagonality and an increase in
14 coefficient of variation, so they -- as the cornea
15 does age, you know, you see these changes and that's
16 in a diabetic population, you know, compared to
17 controls.

18 DR. GRIMMETT: Okay, Dr. Grimmitt again.
19 Then can you infer that a younger cornea, because if
20 its higher reserve, higher cushion, will have a
21 blunted response in terms of hexagonality and
22 coefficient of variation?

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1 DR. EDELHAUSER: Yes, I think you can. I
2 think the corneal endothelial cells are certainly more
3 robust in a younger population and I certainly have
4 seen this in laboratory studies where for example, if
5 calcium free solution is placed on a corneal
6 endothelium and you break the endothelial junctions,
7 the -- in an older cornea, you know, about 40 or so,
8 those junctions won't come back in an in vitro
9 situation but they certainly will with younger tissue.

10 DR. GRIMMETT: Okay. Dr. Grimmatt again,
11 just as a reminder, this study ranged to age 21 or so
12 up to 45 and an average age in the 30s I believe. So
13 from the discussion we've just had, this particular
14 cohort may not show as much change in morphometric
15 parameters as a 60, 70-year old cornea, something like
16 that.

17 DR. EDELHAUSER: Dr. Edelhauser, that's
18 true.

19 DR. WEISS: I just had a follow-up
20 question as far as that goes. For a patient who's
21 destined to develop corneal edema from continued cell
22 loss, would you say 100 percent of the time they're

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1 going have the first sign as a change in the percent
2 hexagonality or coefficient of variation? Is that
3 always the first sign?

4 DR. EDELHAUSER: From our experience, yes,
5 you see this and let me just illustrate it in terms of
6 patients who undergo cataract surgery for example, the
7 -- when the percent hexagonality and the coefficient
8 of variation start to come back or the cells become
9 more regular, the chances of that cornea going onto a
10 post-operative corneal edema are very much less, so
11 you do see that once stability is established, you do
12 have a normal functioning corneal endothelium

13 DR. WEISS: But just in relationship to
14 Dr. Grimmett's point, in a younger patient, it would
15 be -- those changes might be more subtle but would
16 they always be able to be picked up, do you think, as
17 a first sign?

18 DR. EDELHAUSER: They might, but don't
19 forget, this would have to be done with specular
20 microscopy and when you are sampling the cornea, you
21 are taking central corneal endothelial cells in a
22 very, very small population, small area. I mean,

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1 you're roughly counting 100, 150 cells and are looking
2 at the endothelium of that out of a population say of
3 450,000 cells. So you may not pick it up and
4 certainly our past studies have shown that you do see
5 changes in the superior region if you do cataract
6 surgery there. You'll pick that up in the peripheral
7 area very readily where you have damaged the
8 endothelium.

9 DR. WEISS: So it's possible in a younger
10 patient there might be a subtle change in these -- in
11 the coefficient of variation of the percent
12 hexagonality which might not initially be picked up
13 but then later on as things developed got picked up
14 and that could lead to corneal edema.

15 DR. EDELHAUSER: Possibly, yeah, and I
16 mean, it goes in hand in hand with total cell
17 analysis, too, because you know that corneal
18 decompensation is going to occur somewhere between 500
19 and 800 cells per millimeter square.

20 DR. WEISS: Thank you. Dr. Sugar, Dr.
21 Bandeen-Roche, Dr. Matoba and then Dr. Mathers.

22 DR. SUGAR: Two things. One is a comment

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1 on what Dr. Edelhauser said and what he said in his
2 presentation. Certainly, you didn't measure the
3 peripheral corneal endothelial cell densities in any
4 of these patients and presumably the trauma was
5 greatest in the periphery, so that it's conceivable
6 that the central measurements are a distant reflection
7 of what really counts. And I agree that the increased
8 hexagonality and the decreased coefficient of
9 variation over time implies that the endothelial cells
10 in the center are doing better, but you don't -- your
11 reassurance from the data on the periphery is not
12 specifically appropo of this study because you didn't
13 look at it, correct?

14 DR. EDELHAUSER: Yes.

15 DR. SUGAR: The other issue is, I guess
16 for John Vukich. In terms of the powers of the lenses
17 -- I assume we can ask about anything just stick with
18 endothelium.

19 DR. WEISS: Dr. Sugar, you can ask about
20 anything you want.

21 DR. SUGAR: I'll limit myself.

22 DR. WEISS: And that applies to everyone

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1 else on the panel.

2 DR. SUGAR: Okay. When you started this
3 study, did you know that the powers of the lenses that
4 you had were insufficient for totally correcting the
5 patient population that you were investigating? And
6 is -- if that is so, is there an engineering reason or
7 a reason why you didn't have lenses of higher power to
8 correct what you wanted to, that is are there
9 thickness limitations, optic size limitations that
10 keep you from having a higher power?

11 DR. VUKICH: At the time of the initiation
12 of the study, we had anticipated that we would be able
13 to correct the full range. It became clear that at
14 the higher powers the effective power within the eye
15 was less than the engineering estimates and at that
16 point. Due to manufacturing limitations we found that
17 we could only manufacture at that time up to a minus
18 20 lens but the effective power within the eye was
19 approximately 16 to 16-1/2 diopters.

20 At this point those manufacturing
21 limitations are not longer applicable but, of course,
22 that wasn't germane to this clinical trial.

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1 DR. SUGAR: And one other, you said
2 anything?

3 DR. WEISS: Yes.

4 DR. SUGAR: You talk about repositioning
5 lenses and you talk about sizing. Repositioning
6 lenses was for haptics that went in front of the iris,
7 for lenses that propellered, what was that and the
8 sizing, are you talking about vaulting or are you
9 talking about something that doesn't go -- that isn't
10 sufficiently long to be stable or so long that it
11 causes iris bombe (ph) or some other problem?

12 DR. VUKICH: There were four eyes that
13 underwent repositioning. Two of these were for a
14 haptic that was malpositioned, not anterior to the
15 iris but appeared to be folded without flap
16 presentation. One of these was a rotation or actually
17 a decentration, a slight decentration that was
18 recentered without removal and then finally there was
19 one eye that had an edge and one side that captured
20 the pupil in the perioperative area, perioperative
21 period that was readjusted.

22 DR. SUGAR: Did any lenses ever propeller?

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1 Were they ever small enough that they rotated?

2 DR. VUKICH: No, we did not observe
3 rotational changes in any of our patients throughout
4 the course of the trial.

5 DR. WEISS: Dr. Bandeen-Roche?

6 DR. BANDEEN-ROCHE: Karen Bandeen-Roche,
7 and I have a few questions about the specular
8 microscopy. First is a clarification question, so
9 there were 67 eyes followed to four years. As Dr.
10 Grimmett pointed out, two separate 57 patient cohorts
11 preop to four year and three year to four year, and so
12 by my calculations that leads to 47 patients at
13 baseline three years and four years and then two 10-
14 patient cohorts that missed either baseline or three
15 years.

16 And I just want to make sure, by my
17 calculations, the -- and you may need to get somebody
18 to check on this, the mean cell density in that 47
19 patient group was 2496, in the group that did not have
20 the three-year visit, 1779 and in the group that did
21 not have the baseline visit 2269 or I guess rounding
22 up to 2270. And so can someone check whether that's

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1 correct or --

2 DR. VUKICH: We will look into that and
3 have an answer for you.

4 DR. BANDEEN-ROCHE: Okay, now, three quick
5 other questions. First, regarding the plot that Dr.
6 Macsai asked for, what would also be very useful would
7 be to have a plot just like you showed for the 37
8 patient cohort along with overlaid on the same plot,
9 the patients who had three-year data to just compare.
10 Do you know if it's possible to show the panel
11 something like that?

12 DR. VUKICH: We do have that available and
13 can give that to the panel as well.

14 DR. BANDEEN-ROCHE: Okay. I'm interested
15 in how representative the patients with four-year data
16 are of the entire cohort. So that's part of what the
17 first two questions were getting at. Could you tell
18 us the number of investigators who contributed to the
19 67-patient cohort and anything else that would help us
20 about how representative they are besides the anterior
21 chamber depth which we already know about?

22 DR. VUKICH: These eyes were done as a

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1 sub-study and the number of investigators that
2 actually contributed again, I'll have to look up that
3 particular number for you. There were 12 sites that
4 did participate in the entire trial, however. Nine
5 actually did the specular microscopy.

6 DR. BANDEEN-ROCHE: Right, and so the
7 number who actually had four-year data, that would be
8 helpful.

9 DR. VUKICH: Four-year data and we'll get
10 that information. I'm sorry, I don't have that with
11 me.

12 DR. BANDEEN-ROCHE: Okay, thank you. And
13 finally, I guess a question for Dr. Edelhauser.
14 Certainly an unlimited amount of cell loss would not
15 be benign. I mean, could you give me an idea for the
16 degree of cell loss that would be of concern and that
17 would be expected to cause stress independently of
18 hexagonal cells or CV?

19 DR. EDELHAUSER: Well, if we go back and
20 look at the literature, the data that we have in the
21 literature, for example, says that in a normal
22 population, not a high myopic population, the cell

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1 loss per year is .6 percent, and that seems to be
2 consistent, say .6 to 1 percent per year, which goes.
3 The only other comparative data that I can think about
4 as we -- and this is not really the best comparative
5 data, is the data published from Bill Bourne, and this
6 is 10-year data that he has published with various
7 types of intraocular lenses. He's used three
8 different types of lenses. The only trouble with this
9 is that his average age population was 70 at that
10 particular time and he used a medallion iris suture
11 lens. He used a trans-iridectomy clip lens and he
12 used a posterior chamber lens. He could show no
13 difference in cell loss in any one of those three and
14 the cell loss ranged from 2.8, 2.6 and 2.9 percent.
15 So that's kind of the upper level where we do know
16 that if you have that type of cell loss that you still
17 have clear cornea in a 70-year old population.

18 DR. BANDEEN-ROCHE: Thank you.

19 DR. WEISS: Dr. Matoba?

20 DR. MATOBA: Alice Matoba. My question
21 goes back to the age issue raised by Dr. Grimmett.
22 You enrolled patients, ages 21 to 45. Could you tell

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1 us how you selected 45 as the cutoff point?

2 DR. VUKICH: That was the recommendation
3 and guidance of the FDA for enrollment and I believe
4 this was primarily to look at issues of aging as a
5 compounding variable in the formation of lens
6 opacities.

7 DR. MATOBA: And then in your labeling, I
8 notice that the patient information states that you
9 must be 21 to 45 to receive this implant. Does that
10 mean that you intend to limit the use of the implant
11 to patients 45 years or younger?

12 DR. VUKICH: That is the only age range on
13 which we have data to support the safety of this
14 product and would be consistent with our labeling.

15 DR. MATOBA: Okay, and then as the patient
16 ages, what do you think happens to the vaulting,
17 amount of clearance that you have as the lens becomes
18 more nuclear sclerotic with age.

19 DR. VUKICH: Well, we do know that over
20 time we can anticipate an increase in the anterior,
21 posterior dimension of the crystalline lens. We do
22 have information internationally with up to 10 years

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1 of experience that suggests that there doesn't seem to
2 be a significant change in the vaulting
3 characteristics which is somewhat counter-intuitive.
4 We believe that there is also an age related change in
5 the ciliary sulcus diameter as well. And so there may
6 be several things going on at once that can influence
7 the characteristics that fit within the eye over time.

8 Nevertheless, we simply have to accept
9 that as an unknowable piece of information until those
10 time periods have been observed in greater quantities
11 and greater patients have been observed.

12 DR. MATOBA: But you're saying the
13 information you do have indicates that the clearance
14 doesn't change significantly over time.

15 DR. VUKICH: Throughout the course of our
16 trial, which clearly is the best controlled, we have
17 no evidence but again, this is only three years but at
18 this point, we've been carefully monitoring this
19 internationally where there has been longer data
20 follow-up but at this point, we have not seen that as
21 a trend.

22 DR. WEISS: Dr. Mathers, Dr. Schein, Dr.

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1 McMahon and Dr. Grimmett.

2 DR. MATHERS: I have a question for Dr.
3 Edelhauser. If the morphologic change in the
4 endothelium is so sensitive, why doesn't it show
5 something when we know that the endothelial cell count
6 is actually falling by these measurements?

7 DR. EDELHAUSER: Well, I think that you're
8 dealing with essentially a stable -- Dr. Edelhauser --
9 a stable endothelium and the way cells in a normal
10 population that you would see. For instance, we do
11 know we lose cells over a lifetime that if we say .6
12 to 1 percent. We don't see marked changes there
13 either because one, it's an apoptotic change that
14 usually occurs. You're losing a cell. The adjacent
15 cell then slides into then cover up the area and I
16 think that what we're seeing here is just a
17 distribution over the whole surface of the cornea.

18 I can say that we -- I have seen this and
19 we've published papers on this where if you look at
20 the regional areas of corneas. For example, in
21 cataract surgery, if you look superiorly, centrally
22 and inferiorly, you can see these changes markedly and

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1 don't forget, in this study, these -- as these were
2 specular micrographs that were taken.

3 DR. MATHERS: Is your explanation
4 inconsistent with the concept that you could have
5 progressive stable loss rate of one, two, three
6 percent and have a maintenance of a hexagonality as it
7 would be, because the process is essentially just an
8 accelerated but similar to a normal loss rate. It's
9 just faster, so you'd still maintain hexagonality.

10 DR. EDELHAUSER: You could. I mean,
11 again, it's going to depend upon the -- you're
12 expecting a change to occur over the total corneal
13 endothelium and that may not be the specific case that
14 we're seeing.

15 DR. MATHERS: Do you think it would be
16 helpful in understanding what's happening to the
17 endothelium to have images that incorporated more than
18 93 cells on a given patient? It seems to me that when
19 you're looking at the snapshot of the endothelium and
20 as you pointed out, this is a very small area that
21 you're trying to extrapolate then to the entire
22 cornea. Did you only -- for these readings, did you

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1 use the single image for each patient time point or do
2 you use five?

3 DR. EDELHAUSER: We use single image,
4 single image and to answer your question, yes, it
5 would be but the only way that you can get large field
6 or wide field specular micrographs is either with
7 contact specular microscopy and there's no algorithm
8 to go ahead and automatically digitize that other than
9 tracing cells and putting it into a computer, or more
10 recently, there is the possibility of using the
11 confocal and that's certainly a possibility. That
12 gives you a wonderful wide field.

13 DR. MATHERS: You mentioned that you --
14 with Bourne's study on endothelium loss in iris fixed
15 lenses, that sort of thing, that he found a loss rate
16 of 2.7 and it was consistent or that -- and also a
17 clear cornea. You're not maintaining that a loss rate
18 of 2.7 would be able to sustain a clear cornea over a
19 long period of time, I would think. I mean, you're
20 not suggesting that.

21 DR. EDELHAUSER: Well, if you make the
22 assumption that there's not a possibility of some

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1 mechanism to produce more corneal endothelial cells,
2 and I think recent evidence has been shown that ARVO -
3 - that we're seeing is that there is the potential
4 that the peripheral corneal endothelial cells have
5 adult stem cells there. This hasn't been confirmed.
6 There's leading indication that you can measure
7 telomerase activity out there which show -- with
8 telomerase activity you only find in cancer cells and
9 stem cells.

10 You can see that cells do stain with BrdU
11 which is -- and so I think this is a world of research
12 that is developing about the potential of endothelial
13 cells to be replenished.

14 DR. MATHERS: But there is a loss rate at
15 which eventually you will run out of endothelial
16 cells, I'm sure, you maintain.

17 DR. EDELHAUSER: Yes, uh-huh, right.

18 DR. MATHERS: Thank you.

19 DR. WEISS: Dr. Schein?

20 DR. SCHEIN: This is Oliver Schein. I'm
21 going to limit questions or comments to the
22 endothelial area at this time. I remember in 1995

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1 when the first data was presented to the panel on
2 photo refractive keratotectomy there was endothelial
3 cell counts and morphology was performed and the
4 sponsor was pleased and amused to see a large and
5 statistically significant improvement in the
6 morphology from pre-PRK to two years.

7 And this was explained that the majority
8 of individuals before PRK were chronic contact lens
9 users which effected not the cell count but the
10 morphology and the removal of the contact lens allowed
11 the remodeling that appeared favorable over time. Can
12 you please give us some summary of the contact lens
13 wear in this patient population before the surgery and
14 perhaps speculate on how that might impact your
15 estimates of stabilization in the morphology.

16 DR. VUKICH: Let me lead off by saying
17 that contact lens wear was common in our patient
18 population. However, we do not have an exact number
19 of contact lens wearers pre-operatively. That was not
20 recorded as pre-operative entry criteria other than
21 they had to be out of their lenses for six weeks prior
22 to the entry exam. So we have to make the assumption

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1 the majority were. We believe that to be true but we
2 can't give you the percent.

3 We do know that these patients actually
4 showed stability not improvement over time. And so
5 that when we look at the morphometric analysis through
6 time, we did not see a worsening with improvement of
7 a simpler stable population.

8 DR. SCHEIN: But if you're presenting
9 comparison of means, you can't actually determine
10 that. You have to look within subgroups to arrive at
11 such a conclusion. Across an entire population if
12 there is an improvement, that would balance worsening
13 and appear as if there were stabilization.

14 That gets at a second issue. If a
15 majority of the population were wearing contact
16 lenses, that's the acuity that I'd be most interested
17 in as a baseline comparison. It's kind of a habitual
18 vision. It's the vision the patient enters the trial
19 with. The second issue related to endothelial cell
20 count that struck me was not so much the concern about
21 progressive cell loss but of absolute cell loss when
22 you look at the entire cohort. And again, if you

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1 simply present a mean, it doesn't get at the safety
2 issues that we're concerned with.

3 So I interpreted one table as showing that
4 about a third, slightly more than a third of
5 individuals lost 10 percent or more of the central
6 endothelial cell count comparing baseline to three
7 years. Tell me if I've done that correctly. And
8 about 20 percent lost 15 percent or more. Is that
9 correct?

10 DR. EDELHAUSER: I'd have to -- Dr.
11 Edelhauser. Don, you'll have to --

12 DR. SLADE: Steve Slade. While they're
13 getting that, I might just address, Oliver, your point
14 about the contact lens being the habitual vision,
15 that's a good point. On the other hand, this was
16 developed with best spectral visual acuity as a
17 target with FDA guidance and, of course, as a standard
18 for refractive surgery and if you look at the
19 patient's satisfaction rates, they were very high and
20 if they were comparing their post-operative vision to
21 what they were used to in contact lenses, and if that
22 were markedly better and we had reduced them, I don't

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1 think the satisfaction rates would have been quite so
2 high.

3 DR. SCHEIN: You've got me now on
4 digression which I wasn't going to raise now. The
5 satisfaction scale that you use appeared to only have
6 three options which doesn't give a lot of room a very
7 strong ceiling and floor effect with only three
8 options for a response. And there are at least two
9 well validated, available, three kinds of visual
10 function questionnaires directed towards populations
11 like this that I think could be used to get more
12 detail.

13 DR. WEISS: I would ask -- I would have
14 the sponsor just given the advantage of not having to
15 identify themselves any more because I'm told the
16 transcriptist knows your voice. I would also ask the
17 panel members if we could limit our questions because
18 now we're over. So if we could just get to the cogent
19 points quickly and give the sponsor the ability to
20 answer those. Are there any other questions you have
21 Dr. Schein?

22 DR. SCHEIN: I'm just waiting for the --

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1 was I correct on the endothelial cell count?

2 DR. SANDERS: Yeah, I believe you were
3 correct on the numbers. I think one has to remember
4 that that was the cumulative -- you were talking the
5 cumulative loss between pre-op to three years.

6 DR. SCHEIN: Correct.

7 DR. SANDERS: Yes. And again, I think we
8 have to also keep in mind that some of that -- given
9 that the counting variability is eight to 10 percent,
10 that that enters into the equation, the numbers you
11 did give us are very similar to what we would
12 calculate.

13 DR. WEISS: Dr. McMahon, Dr. Grimmett, Dr.
14 Coleman, Dr. Ho, then Dr. Macsai and Dr. McCulley.

15 DR. McMAHON: Dr. McMahon. This is a
16 question for Dr. Vukich. I believe two and a half
17 percent of implanted lenses were implanted initially
18 up side down. And the majority of those, I believe
19 occurred in the first 10 cases, though in Dr.
20 Grimmett's review he pointed out that a number of them
21 occurred downstream. The question I have, is this an
22 issue of surgical training or is this an issue where

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1 the device needs to be more clearly labeled as to
2 which is right, left, to minimize those sorts of
3 things?

4 DR. VUKICH: There's clearly a learning
5 curve in this, in that half of these did occur early
6 in the experience, within the first eight cases of any
7 individual surgeon. This technique is an important
8 part of our training program. We've identified that
9 if this lens is loaded properly and carefully under
10 the microscope in the cartridge, that we can
11 significantly minimize the risk of an uncontrolled
12 entry into the anterior chamber. And so I believe
13 firmly that this is something that can be controlled
14 and in fact, in my personal experience of having put
15 90 of the lenses in at our site, not a single one went
16 in up side down. I'm also in charge of the training
17 to address this issue. So I think it is something
18 that clearly is a concern but we believe it's an issue
19 that isn't a matter of identifying the right side up.
20 It's just a matter of doing it properly in the first
21 place.

22 DR. WEISS: Dr. Grimmett.

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1 DR. GRIMMETT: Michael Grimmatt. Dr.
2 Slade mentioned that this study was IDE-approved in
3 1995. What was the first date of the V4 lens
4 implantation? Quite a bit later?

5 DR. SLADE: All of the -- Steve Slade. I
6 believe all of this data was before.

7 DR. GRIMMETT: Correct, '89, '99 something
8 like that?

9 DR. SLADE: '98.

10 DR. GRIMMETT: '98, okay. Was gonioscopy
11 performed on any patient in this study?

12 DR. SLADE: Gonioscopy was performed on
13 all patients preoperatively in this study.

14 DR. GRIMMETT: Preop, okay. I didn't note
15 it on the clinical study report form or in the PMA
16 materials. You have that somewhere then. We just
17 didn't see it; is that correct?

18 DR. VUKICH: Dr. Vukich. It was on the
19 preoperative checklist for inclusion in the study and
20 gonioscopy was required for every patient as an entry
21 criteria.

22 DR. GRIMMETT: Okay, good, but just to

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1 confirm it was not performed post-op on any patient.

2 DR. SLADE: It was not a required
3 examination.

4 DR. GRIMMETT: Okay, was angle anatomy
5 viewed with ultrasound in the ultrasound sub-study?

6 DR. VUKICH: Yes, it was.

7 DR. GRIMMETT: It was, good. Was the data
8 in the PMA somewhere?

9 DR. VUKICH: It was not.

10 DR. GRIMMETT: It was not, okay. Of the
11 up side down lens insertions that we just heard about
12 from Dr. McMahon, were they related at all to using
13 the plunger versus the screw injector style, like 13
14 used plunger and 3 used the screw injector?

15 DR. VUKICH: We did look at that as a
16 variable and we are unable to look at any evidence
17 that the screw -- that the actual injection mechanism
18 itself was a factor. Again, we firmly believe that it
19 was how the lens was loaded in the cartridge as
20 opposed to how it is pushed through the cartridge.

21 DR. GRIMMETT: Okay.

22 DR. SLADE: It might be worthwhile -- the

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1 lens, it's very apparent, the lens because of the
2 vault, because of the markings before you load is
3 which is right side and which is not. And the
4 cartridge is the same whether you use it with the
5 screw type injector or the plunger.

6 DR. GRIMMETT: Okay, all right. Your
7 materials indicate your white-to-white measurements
8 had an accuracy of a tenth of a millimeter. My
9 Castroviejo's calipers in the OR have an accuracy in
10 one millimeter increments. What calipers were you
11 using to get .1?

12 DR. VUKICH: The same ones you are.

13 DR. GRIMMETT: Oh, okay.

14 DR. VUKICH: Calibrate them against the
15 steel rule under a microscope.

16 DR. GRIMMETT: But they're only one
17 millimeter increments. So any unit underneath one
18 millimeter is a shear guess; isn't that correct?

19 DR. VUKICH: There would be an estimate,
20 yes, below that level, correct.

21 DR. GRIMMETT: Okay, I've used them and,
22 boy, when I want them at 3.3, it's awful hard to set

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1 it at that. And I guess my last question I'll make
2 it, I'll just skip some of these, we'll get to it
3 later, in your materials you stated that your version
4 4 lens has an additional .13 to .21 millimeters of
5 vault compared to version 3. And I was just curious,
6 did you substantiate that by in vivo measurements or
7 was this a design parameter and you postulated it or
8 how do you know that?

9 DR. VUKICH: It was a manufacturing and
10 design parameter. This is an engineering issue.
11 External to the eye, this would be the vault that was
12 designed.

13 DR. GRIMMETT: Okay, thank you very much.

14 DR. WEISS: Dr. Coleman?

15 DR. COLEMAN: This is Dr. Coleman and I
16 have a question about two of your subjects developed
17 glaucoma in this study and I was questioning how you
18 define glaucoma. Was that based on optic nerve
19 changes or visual field loss?

20 DR. VUKICH: Actually, two of our patients
21 were treated with beta blockers, neither of which
22 showed optic nerve changes or visual field changes.

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1 So I think they would be best categorized as ocular
2 hypertensive so there was not the diagnosis of visual
3 field loss or glaucoma as we would classically define
4 it.

5 DR. COLEMAN: You might want to change
6 that. In addition, you said that you did do angle
7 morphology via ultrasound but that's not available in
8 the PMA. Is that --

9 DR. VUKICH: That angle was observed.
10 There was a sub-study of forty patients that were
11 observed with a P40 unit, a Paradigm unit and we did
12 look at angle morphology. There is within the PMA a
13 description, pictures as well as a commentary of the
14 results of that study.

15 DR. COLEMAN: Okay, and then in terms of
16 post-operative gonioscopy was not done, not even in
17 the subjects who were diagnosed with glaucoma or is
18 that not available or --

19 DR. VUKICH: That information was not a
20 required part of the post-operative follow up and I do
21 not have that information as part of the PMA.

22 DR. WEISS: Dr. Macsai?

1 DR. MACSAI: My questions are mostly to
2 Dr. Edelhauser again. Sorry, Hank.

3 DR. EDELHAUSER: No problem.

4 DR. MACSAI: When this lens is inserted,
5 the most damage to the endothelium should occur in the
6 periphery. If the surgeon is following the technique,
7 they're not supposed to go anywhere near the central
8 cornea. It's defined as a no-touch zone. The
9 manipulation of the haptics is done way at the
10 periphery and they're tucked under the iris with a
11 little lens manipulator, haptic manipulator device as
12 Dr. Slade showed us in his slide. So given that and
13 the presentation you've said about how the peripheral
14 endothelial cell counts is greater than the central in
15 your well-established published articles, and the fact
16 that we're talking about implanting this in 22-year
17 old patients, I have some level of confusion I'm
18 asking you to help me with.

19 In a guidance draft from a meeting in
20 10/02 accepted endothelial cell loss rate was 1.5
21 percent, yet in an ANSI document that I think is also
22 a draft, it was set at two percent. So let me ask

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