

1 present it only because our presentation was geared towards
2 the basic safety and effectiveness parameters.

3 CHAIRMAN McCULLEY: Well, you're supposed to
4 present your whole submission and issues related to your
5 submission that are of importance.

6 DR. McDONALD: I'm sorry, Dr. McCulley. We were
7 digging for data here. But for the times when there was
8 some induced astigmatism, we don't have an explanation at
9 this point.

10 DR. MAGUIRE: The next--can I still keep going?

11 CHAIRMAN McCULLEY: Yes.

12 DR. MAGUIRE: The next question is: In the
13 presentation, it shows that corneal topography is one
14 component of the presentation, and I think the comment in
15 the material says something like corneal topography will be
16 done on people who have anomalous or unusual results. I
17 would certainly think that an induced astigmatism of 1 to
18 1.5 diopters would be something that would trigger that.
19 And so the question is: Was there any kind of topographic--
20 or we also know you have Hartmann-Shack (ph)-type analysis
21 available, at least at some of the sites and so on. Do you
22 have any objective measures of either corneal topography or
23 optical performance that could explain this rate of induced
24 astigmatism in a group of people that had no myopic
25 correction--I mean, no astigmatic correction?

1 DR. McDONALD: Dr. Maguire, this week we did pull
2 the charts on all patients who had greater than 1 diopter of
3 induced astigmatism postoperatively at any time point, and
4 we looked to see if we could analyze the topography
5 pictures, some of which were taken with ISIS and some of
6 which were taken with TMS-1 or TMS-2. And the presentations
7 were presented with an opaque color map in all three
8 instances over the black and white picture of the eye with
9 the placito rings. And we looked to see if we could find
10 perhaps displacement, decentration as the cause, but we were
11 unable to find that information because only if you have the
12 translucent color map can you still see the center of the
13 entrance pupil behind it.

14 However, I did look at them, and I could not see
15 displacement of a clinically noticeable magnitude in any of
16 the pictures that I saw.

17 DR. MAGUIRE: Did you see induced astigmatism?

18 DR. McDONALD: Some of the maps you could see had
19 some cylinder, yes, but I could not say that it was because
20 of decentration.

21 DR. MAGUIRE: Yes, because--

22 DR. McDONALD: It showed the cylinder. You could
23 see the cylinder on the map, but nothing like decentration
24 as the cause.

25 DR. MAGUIRE: So it was regular induced

1 astigmatism?

2 DR. McDONALD: Yes, regular bow-tie--

3 DR. MAGUIRE: Okay. So it's fair to say that
4 someone who had absolutely no astigmatism before surgery can
5 have an ablation that's supposed to give a uniform ablation
6 with no astigmatic correction, and one can see 7.5 percent
7 incidence of an induced regular astigmatism of 1 to 1.5
8 diopters. Is that correct?

9 DR. McDONALD: At which time interval, Dr.
10 Maguire?

11 DR. MAGUIRE: I'm looking--well, let's see. When
12 I reviewed this it was Tab A.2, page 46 or Table 46 in the
13 big folder here.

14 [Pause.]

15 DR. McDONALD: What time interval, again, Dr.
16 Maguire? We've got Table 36 now, Section A.2, page 46; 3.4
17 percent at 1 month at greater than 1, and 4.7 percent at 3
18 months, 3.2 percent at 6 months.

19 DR. SALZ: We see that with myopic corrections at
20 times, also, in a small number of cases.

21 CHAIRMAN McCULLEY: That's a little bit high, the
22 percent.

23 DR. SALZ: I would agree it's a little higher than
24 you see in the myopes.

25 DR. MAGUIRE: Yes. If you add 0.7--if you add the

1 increase of 1, 1.5--1.25 and 1.5 diopters at 1 month,
2 that's, what, 6.7--that's 7.4 between 1 and 1.5 induced. At
3 3 months with a smaller n, obviously--

4 DR. SALZ: He's including 1 or more.

5 DR. MAGUIRE: Okay. So those numbers, if you
6 take--increased 1.0 diopters, increased 1.25 diopters, and
7 increased 1.5 diopters, you have a 7 to 8 percent incidence
8 of induced astigmatism at all time charts measured here.

9 CHAIRMAN McCULLEY: Again, I think it's a good
10 point--

11 DR. MAGUIRE: So it's at least a labeling issue.
12 I'm not saying that--

13 CHAIRMAN McCULLEY: This is a good point. It
14 doesn't go beyond guidance, but it is an important point
15 that would be important for labeling.

16 DR. MAGUIRE: And it's also an efficacy issue. In
17 other words, one of the things that's interesting about this
18 is we've had corneal topography available for a long time,
19 and because there are kind of standardized ways that the FDA
20 does things--and I respect that and I respect the fact that
21 industry is following orders and following a standardized
22 process. And this isn't meant as any accusatory thing, that
23 you're doing anything less than FDA asks. But it is a
24 question of, as Dr. Macsai has said, patient satisfaction
25 and patient expectations, and it should show up, and it is

1 something that we have to consider in efficacy.

2 CHAIRMAN McCULLEY: We have, since the beginning
3 of the excimer laser PMAs, tried to make sense and use out
4 of topography and, despite everyone's valiant try, have not
5 been able to do it except when there's been something
6 unusual that the topography has helped us maybe identify the
7 decentration or the irregular astigmatism. Other than that,
8 the standard analysis of topography has given us virtually
9 nothing.

10 DR. MAGUIRE: There's some truth to what Dr.
11 McCulley says, and yet at the same time, it's been valuable
12 here, and the presenters have used it effectively to show
13 that their problem in these cases is one that the ablation
14 is giving an astigmatism different than they expected, not
15 that there's a decentration problem.

16 CHAIRMAN McCULLEY: Right

17 DR. MAGUIRE: And certainly that's very useful
18 information, rather than just dealing with indirect evidence
19 and shrugging and saying, gee, we don't know why we have
20 this efficacy problem with induced astigmatism.

21 CHAIRMAN McCULLEY: Well, they know that it's not
22 decentration. They know that they're getting truly induced
23 regular astigmatism based on what was said. So in applying
24 topography there, it let us know that it was not an
25 aberration in the treatment. Nothing went awry. It's just

1 that it was induced. And then the question would be: Why
2 was it induced? And I don't know that we've heard an answer
3 to that except they don't know

4 DR. MAGUIRE: But I think it's an important issue
5 to bring up, especially with the technology that claims to
6 give an extremely precise ablation pattern.

7 CHAIRMAN McCULLEY: Well, it becomes--I mean, it's
8 not outside of guidance, so it would be something that would
9 be important to include in labeling

10 DR. MAGUIRE: I agree.

11 CHAIRMAN McCULLEY: And we can talk further about
12 it if we think it's more of an efficacy issue or safety
13 issue later.

14 Marian?

15 DR. MACSAI: Well, I think that you've both made
16 interesting and important points. We realize now that this
17 is not from decentration with the tracking system. This was
18 not a problem, according to Dr. McDonald. However, it
19 appears to be a nomogram problem. One out of four patients
20 that are spheres end up astigmats if you consider a half
21 diopter, as the sponsor has told us, is within the limits of
22 human error and refraction to be induced astigmatism.

23 So I think that Dr. Maguire has made a very
24 important and perhaps safety and efficacy point of 25
25 percent, regardless of the guidance document. And you just

1 said, Dr. McCulley, that the guidance document is a loose
2 document at this range because we wouldn't be pinned down
3 because of these sorts of issues. So I don't think we can
4 shove this under the table.

5 CHAIRMAN McCULLEY: I'm not trying to shove it
6 under the table. And I'm not sure what table it belongs on.
7 My initial response would be it belongs on the labeling
8 table, and certainly on the labeling table. Whether we
9 think it belongs on the safety and efficacy table, we'll
10 deliberate further on in our discussions. So don't
11 misinterpret--I don't know where you get the "shove under
12 the table" bit, but there ain't nothing trying to be shoved
13 under any table.

14 There was another hand over there around Marian.
15 Mike?

16 DR. GRIMMETT: It looks like the sponsors are
17 going to respond to the prior question.

18 DR. McDONALD: In two parts, actually. The Eye
19 Care Technology Forum in '97 did attempt to see whether
20 topography could help in analysis of induced astigmatism,
21 and though they are different group, they did decide to look
22 at greater than 2 diopters of induced cyl as a performance
23 criteria because they felt that was the level at which it
24 was very clinically significantly and perhaps starting to
25 even impact BSCVA.

1 DR. SALZ: Well, the other thing, the surgeon had
2 the option in the spherical group of correcting small
3 amounts. In other words, some people had half to three-
4 quarters of cylinder, and it was not attempted to correct
5 it. Do you have that number?

6 CHAIRMAN McCULLEY: So you'd have to look at
7 difference pre- to postop--

8 DR. MAGUIRE: But your thing specifically talks
9 about induced astigmatism, which is different than pre-
10 existing astigmatism.

11 CHAIRMAN McCULLEY: So presumably you did your
12 data long the lines of your definitions that it increased
13 it.

14 Arthur? Oh, I'm sorry, Mike. Yes, you got
15 sidetracked.

16 DR. GRIMMETT: Thank you. Just a follow-up to the
17 prior question of Dr. Macsai's where she was talking about
18 the accuracy of refraction plus or minus a half when it was
19 stratified by cylinder, the groups that didn't reach it we
20 were saying was--reach the target values, that is, was the 3
21 to 3.99 group. My question is: In that group, because
22 stratifying by cylinder does not precisely describe the
23 totality of refractive ablation, it's just a way of putting
24 things into bins, I'm wondering does that group have
25 something different about it in terms of the amount of

1 sphere, perhaps? Did you pull out those eyes and look at
2 them for any differences in that regard?

3 DR. STEVENS: I can take a look at it. I haven't
4 looked at it so far.

5 DR. GRIMMETT: Okay. Thank you.

6 CHAIRMAN McCULLEY: She said she'd look at it.
7 And you're going to get back to us after--you're going to
8 look at it now. Okay.

9 Arthur?

10 DR. BRADLEY: A continuation on the issue of
11 astigmatism and induced astigmatism, two points, really.
12 One, to continue the table metaphor, I suspect there is
13 another table involved here in the sense that if the panel
14 highlights an issue like this, it's not simply a matter of
15 patient labeling, but also it's feedback to the sponsor that
16 there may be something awry with the procedure and that they
17 should take note of that. So that was the first point.

18 I think the second point is a general question
19 that I think the sponsor has seen my review of this report,
20 and here we are again struggling with the astigmatic
21 problem, and we keep--the sponsor's presentation this
22 morning even highlights the problem with astigmatic data
23 sets. What do you do? Do you group them by spherical
24 equivalent? Do you group them by astigmatic amplitude? Do
25 you group them by astigmatic axis?

1 We essentially are taking a three-dimensional data
2 set, compressing it down to one dimension, and trying to do
3 some sensible analysis on that. And in the end, we're sort
4 of at a loss, and here's a perfect example. Dr. Maguire has
5 pointed out that we have this induced astigmatism. We don't
6 really know why, and it's not clear from the report whether
7 that same factor, whatever it is, is a component in the
8 reduced efficacy that we see with the high astigmats. Is it
9 the same factor that's inducing astigmatism in the spherical
10 eyes that's reducing the efficacy in the high astigmatic
11 eyes?

12 When you break out the data into these one-
13 dimensional metrics, I don't think you can really discover
14 that. I think you need to embrace the full three-
15 dimensional nature of that data set to look if there is a
16 bias in the data, and it could be something to do with the
17 algorithm, as Dr. Macsai suggests. I'm not saying that it
18 is that. At this point I'm not sure we know. And it may be
19 there could be a unifying explanation to a lot of these
20 astigmatic problems, whether it's either induced astigmatism
21 or the reduced efficacy of correcting high astigmats. But I
22 don't know that.

23 CHAIRMAN McCULLEY: Was that a statement
24 requesting response from sponsor?

25 DR. BRADLEY: It wasn't requesting a response, but

1 it's just a commentary. They've already seen the question.

2 CHAIRMAN McCULLEY: Okay. If you would like to
3 respond to that, please do so.

4 DR. APPLGATE: Ray Applegate. I'm a paid
5 consultant to Autonomous. I think Arthur does raise a good
6 point in terms of the three-dimensional graphing of it along
7 the methods of Tibus (ph) and others. I would note that
8 what's particularly perplexing about the issue is where do
9 we draw the line between what impacts on visual performance
10 and actually will cause a safety concern. And that's where
11 we have to address the question of how fine a comb do we
12 want to put on, and I love the analogy of my very first
13 patient. I'm an optometrist trained at Indiana and a Ph.D.
14 from Berkeley. And my very first patient was a young woman
15 who was about a 3 diopter myope spherical, and I could get
16 her down to better than 20/15, but she was very unhappy with
17 the 20/15 vision because everything was so sharp and she
18 could see the blemishes on her boyfriend's face across the
19 room and liked it softer.

20 So the question really, in my mind, that I
21 struggle with is: When is there a safety issue? We go down
22 to the driver's license all the time and get a driver's
23 license with 20/40 and we drive a five-ton vehicle around
24 that can kill instantly, and we consider that safe.

25 CHAIRMAN McCULLEY: Can I ask you not to--I mean,

1 we got into commentary here which we really shouldn't have,
2 but I've got to stop it somewhere.

3 DR. APPELEGATE: I appreciate that.

4 CHAIRMAN McCULLEY: So let's--if you can respond.

5 DR. APPELEGATE: I'll try to focus in.

6 CHAIRMAN McCULLEY: Yes.

7 DR. APPELEGATE: So I would ask in this room how
8 many people are ideally corrected right now that know that
9 they're ideally corrected, have residual error?

10 CHAIRMAN McCULLEY: We're not taking straw polls
11 here. Will you please--

12 DR. APPELEGATE: All right--

13 CHAIRMAN McCULLEY: --respond directly to the
14 subject on the floor?

15 DR. APPELEGATE: I guess my--the subject on the
16 floor is three-dimensional analysis, and I want to be--and I
17 think it's very important, and the sponsors are moving in
18 that direction to look at that type of analysis to improve
19 performance.

20 But what we need is guidance and understanding
21 from the FDA's point of view of what is a significant loss
22 that poses a safety problem?

23 CHAIRMAN McCULLEY: Okay. Thank you.

24 I think that astigmatism gives us troubles at
25 times. Do you want to--

1 DR. ROSENTHAL: Well, I think it's only fair to
2 have to go back to a guidance document, and the guidance
3 document has been an induced astigmatism of greater than 2
4 diopters in those patients--an induced astigmatism of
5 greater than 2 diopters increase in those patients. That is
6 what the guidance document has said, and that has been
7 established based upon a consensus between the agency, the
8 practicing community, and the industrial community.

9 CHAIRMAN McCULLEY: Right.

10 DR. ROSENTHAL: And I think these are all very
11 important issues, but I think they may--and I appreciate
12 them being pointed out, and they can be dealt with. But you
13 have to decide as a panel whether or not these are issues
14 that should mitigate a change in the guidance document.

15 CHAIRMAN McCULLEY: Okay. Again, we've gotten two
16 things going here that have become fairly clear.

17 One is safety and efficacy relative to the
18 guidance document that is a guidance that we're all bound
19 by. And if we don't like it, we need to change it.

20 The other issue, as I see it, is one that relates
21 to labeling for physician and patient sake, and that one is
22 not bound by numbers in the guidance document. And Leo had
23 pointed out something very important.

24 Then there are all of these issues that, you know,
25 making a perfect world, that relate to astigmatism that

1 really isn't necessarily for us in this forum discussing a
2 PMA to deal with.

3 DR. ROSENTHAL: But, Mr. Chairman, as you have
4 pointed out, it is a guidance document. If the panel feels
5 that the levels that are reached are unacceptable regardless
6 of what the guidance document says, they have a right to
7 express that opinion in this public forum.

8 CHAIRMAN McCULLEY: I agree, and we will discuss
9 that when we get to, you know, how we're dealing with our
10 recommendations specifically related to this PMA.

11 Dr. Pulido?

12 DR. PULIDO: I would say that to ask from sponsor
13 data that we've not asked from others is not acceptable at
14 this time, but I would recommend to Dr. Rosenthal to accept
15 Dr. Maguire's suggestion that we have some kind of a forum
16 here where we discuss adaptive optics and become all better
17 informed on adaptive optics and the new data that that can,
18 therefore, bring into this and hopefully incorporate that
19 into future documents.

20 CHAIRMAN McCULLEY: I think that would be from,
21 you know, Arthur's and Leo's comments, but this is not the
22 forum in which we should be doing that today.

23 Now, any more questions for sponsor?

24 [No response.]

25 CHAIRMAN McCULLEY: I would like to give sponsor

1 now the opportunity to make their closing comments before
2 being excused from the table. Do you have any closing
3 comments?

4 MS. McGARVEY: Shirley McGarvey, regulatory
5 consultant to ATC.

6 We appreciate the comments that speak to
7 evaluations within the context of the guidance and more
8 finely tuning that guidance, and we encourage that that
9 should occur.

10 We would also just like to point out that one
11 other point was made that in our original submission 75
12 percent of the population was available at 6 months. The
13 update, we have approximately 90 percent of the population
14 at 6 months is in that update.

15 CHAIRMAN McCULLEY: Your presentation today was 75
16 percent.

17 MS. McGARVEY: In the update, I believe that we
18 had 332 of 360 eyes.

19 CHAIRMAN McCULLEY: I'm surprised you didn't
20 present that rather than presenting the 75 percent.

21 DR. PULIDO: It was presented.

22 CHAIRMAN McCULLEY: It was, but it stated 75
23 percent at 6 months.

24 MS. McGARVEY: That was because our first part of
25 the presentation spoke to the submission that we had filed

1 with--attempting to--

2 CHAIRMAN McCULLEY: Okay, so it's 90 percent--

3 DR. ROSENTHAL: They did exactly what they were
4 told. They presented the submission as it was--

5 CHAIRMAN McCULLEY: Okay, I got confused by--

6 MS. MCGARVEY: I just wanted to make that clear.

7 DR. ROSENTHAL: --the comments to the reviewers
8 with their update.

9 MS. MCGARVEY: Correct.

10 DR. MAGUIRE: Dr. Rosenthal, isn't it also true
11 that 13--13.9 percent are in process. Okay? In other
12 words, when I look at the slide that was presented, at 6
13 months 75.3 percent available for analysis, 5.6 percent
14 discontinued, 13.9 percent in process--

15 DR. ROSENTHAL: Can you tell me which--I'm sorry,
16 Dr. Maguire?

17 DR. MAGUIRE: It's in Dr. McDonald's presentation.

18 DR. ROSENTHAL: Which page

19 DR. MAGUIRE: Accountability--it looks like the
20 back of page 7, I think. These aren't numbered in order,
21 so--

22 Ms. MCGARVEY: That is true.

23 DR. ROSENTHAL: Let me again make a comment about
24 accountability, which we've been through. The panel has
25 requested an accountability by the FDA definition. You go

1 by FDA definition of 90 percent. The office has said that
2 compared to other areas within the Office of Device
3 Evaluation it's slightly high, and the office has been
4 accepting around 80 percent accountability.

5 CHAIRMAN McCULLEY: Your office.

6 DR. ROSENTHAL: The Office of Device Evaluation.

7 MS. MCGARVEY: Other specialties.

8 DR. ROSENTHAL: Other specialties. So that, I
9 mean, obviously 100 percent accountability would be optimal
10 in all these studies, but we have to--you know, we have to
11 go with what is acceptable practice.

12 I don't know what the new accountability numbers
13 are.

14 DR. STEVENS: In the updated cohort at 6 months,
15 there's 89 percent of the eyes available. That's all that
16 will be available because 5.6 percent were discontinued for
17 retreatment at 3 months, and the remaining 5 percent were--
18 they missed a visit.

19 CHAIRMAN McCULLEY: Did you present data today on
20 that 89 percent?

21 DR. STEVENS: We presented the updated--

22 MS. MCGARVEY: Yes. Both were presented today.

23 CHAIRMAN McCULLEY: Okay. Because--

24 DR. ROSENTHAL: And let me point out again that
25 their accountability, even in the new data, is above 90

1 percent by our definition of accountability. You can't take
2 the retreated and include them. It's not fair. They've
3 been taken out completely. They can't be evaluated. So--

4 CHAIRMAN McCULLEY: I think that, you know, what
5 my point would be, if the percentage of patients that are
6 appropriately available at 6 months or will be available,
7 what that percentage is, not jacking around with any of
8 these definitions or yours or how you would define them, but
9 what percentage of the patients that would be appropriately
10 available for evaluation at 6 months were presented.

11 DR. ROSENTHAL: Right. That's pretty much our
12 definition of accountability, so that those who haven't
13 reached 6 months, we can't include them in the--

14 CHAIRMAN McCULLEY: Well, no. If they're in the
15 pipeline and they just haven't reached 6 months, then you
16 wait until 6 months on them.

17 MS. MCGARVEY: However, what happens is that
18 patients may be eligible for a particular interval window.
19 They may not yet have been evaluated, but they have not yet
20 missed that visit at the time we freeze the database. That
21 speaks to that 13 percent number. That's not an uncommon
22 level that occurs at a further out data point.

23 What we have now in the updated 6-month data
24 provided is approximately 90 percent of the patients with
25 data at 6 months, and as we showed, comparing the

1 information in the submission and the 6-month update, the
2 data is basically further reinforced. We saw no differences
3 from the update. We just had more numbers that continued to
4 confirm the 6-month performance.

5 CHAIRMAN McCULLEY: Okay. Let me make sure I'm
6 clear. Of the patients that entered the study--

7 MS. MCGARVEY: Yes.

8 CHAIRMAN McCULLEY: --that have not been lost to
9 follow-up or died or had MIs or been retreated, so that
10 number, whatever that number is, how many of those have been
11 evaluated at 6 months--or not been evaluated at 6 months
12 because they haven't reached the 6-month window?

13 MS. MCGARVEY: I believe the updated 6-month
14 patient number is--the number of eyes is 332 out of 360
15 enrolled.

16 CHAIRMAN McCULLEY: Okay.

17 DR. MATOBA: I have two questions. One is
18 regarding the monovision people. They're not--they're in
19 that 340, but they're not really analyzed in the--

20 MS. MCGARVEY: They're always analyzed in the
21 accuracy and precision of sphere, cylinder, and MRSE. They
22 are only not analyzed within the uncorrected VA numbers
23 because their intent was not final. That's all. And that's
24 the convention that has been followed in reporting all key
25 variables.

1 CHAIRMAN McCULLEY: Dr. Rosenthal?

2 DR. ROSENTHAL: Are you still in the question and
3 answer period that I may--

4 CHAIRMAN McCULLEY: Well, we apparently are, yes,
5 because--

6 DR. ROSENTHAL: Okay.

7 CHAIRMAN McCULLEY: I'm going to be a little
8 flexible with this because there are some issues here. One
9 other question.

10 DR. MATOBA: I'd like to ask Dr. Rosenthal why we
11 don't mandate that retreatments be deferred until a certain
12 time period has elapsed, say a minimum of 6 months or 9
13 months, or whatever time interval we want the follow-up to
14 be? Well, 3, but then you don't have stability data.

15 DR. ROSENTHAL: We take each consideration into
16 account. It depends on the results.

17 CHAIRMAN McCULLEY: Okay. Let's go back to
18 Shirley--

19 DR. ROSENTHAL: And some sponsors are never
20 allowed to retreat, and other sponsors are allowed to
21 retreat based upon their preliminary data.

22 MS. MCGARVEY: Those are my only points, was to
23 just point out that we do have more patients at 9 months--
24 excuse me, at 6 months, but also that we do believe that
25 further attention within the context of the guidance is

1 appropriate.

2 CHAIRMAN McCULLEY: Thank you.

3 Let's a 15-minute break. Parkinson got us, and we
4 were an hour ahead. Now we're right on time. So we
5 reconvene at 11:45.

6 [Recess.]

7 CHAIRMAN McCULLEY: Okay. We're going to
8 reconvene on PMA P970043/S7, and now we are going to have
9 the FDA presentation. Morris, this is your division. You
10 are sitting in the back, so I guess you're letting others do
11 the work. Quynh, you or Malvina? Quynh?

12 MS. HOANG: Yes, sir. Thank you, Dr. McCulley.

13 The LADARVision Excimer Laser System from
14 Autonomous Technologies Corporation, under PMA application
15 P970043, was approved on November 2, 1998, for the
16 indication of photorefractive keratectomy for the reduction
17 or elimination of mild to moderate myopia of between -1.00
18 and -10.00 diopter sphere and less than or equal to -4.00
19 diopters astigmatism at the spectacle plane, the
20 combination of which must result in an attempted correction
21 of between -0.50 and -10.00 spherical equivalent at the
22 spectacle plane where the sphere or cylinder is at least 1
23 diopter.

24 The sponsor submitted the current supplement to
25 the PMA application, Supplement 7, to further expand the

1 indication statement. The FDA team that reviewed Supplement
2 7 included Dr. Malvina Eydelman, Dr. Bruce Drum, Dr.
3 Hollington Lu, Ms. Carol Clayton, and myself. Dr. Eydelman
4 will now present the areas in which your input is being
5 requested.

6 DR. EYDELMAN: Good morning. I would like to
7 thank the sponsor for providing me with a draft copy of
8 their presentation prior to the meeting, allowing me to
9 avoid redundancy in my presentation. Today I will,
10 therefore, only highlight some points for panel
11 consideration and will not present a comprehensive review of
12 the clinical studies in this PMA.

13 Autonomous Technologies Corporation requests
14 approval of LADARVision Excimer Laser System for LASIK
15 treatments for the reduction or elimination of hyperopia up
16 to +6.00 diopters with up to -6.00 diopters of astigmatism
17 at the spectacle plane.

18 Within the requested indication, as specified by
19 the sponsor, there are three types of refractive errors
20 being treated: spherical hyperopia, hyperopic astigmatism,
21 and mixed astigmatism. Mixed astigmatism refractive error
22 is defined as the presence of hyperopic refractive error
23 along one meridian and the myopic refractive error along the
24 orthogonal meridian.

25 While the Ophthalmic Panel has previously

1 considered a PRK application for spherical hyperopia, this
2 is the first application for LASIK spherical hyperopia. It
3 is also the first time the panel is being asked to consider
4 hyperopic astigmatism and mixed astigmatism. Furthermore,
5 while analysis and desired outcomes for hyperopic
6 astigmatism were previously pondered by the panel in the
7 content of updating the refractive guidance for excimer
8 lasers, mixed astigmatism and its appropriate analysis and
9 endpoints have not been previously discussed at the panel
10 meeting.

11 My written review was based on the analysis of the
12 original and all the amendments received by FDA as of
13 February 7, 2000. On February 21, the sponsor has submitted
14 an unsolicited amendment responding to the issues discussed
15 in my written review. In this amendment, stability analysis
16 was recalculated based on updated 9 months consistent cohort
17 of 131. On March 1, the sponsor has submitted another
18 unsolicited amendment in order to respond to concerns raised
19 by the primary panel reviewers. This amendment included an
20 updated key safety and efficacy analysis table for the
21 overall cohort with n of 321 at 6 months and 144 at 9
22 months. My comments today will incorporate all data
23 available to FDA at the present time.

24 Dr. McDonald has already mentioned some of the
25 stability analysis based on 6 months consistent cohort. I

1 will reiterate some of the relevant numbers. This slide
2 presents analysis of the original 6 months consistent
3 spherical cohort comprised of 123 eyes. As you can see,
4 between 1 and 3 months, 95.9 percent of the eyes had a
5 change in MRSE less than 1 diopter. It was a mean
6 difference of 0.12 diopters or 0.06 diopters per month.
7 Between 3 and 6 months, change in MRSE remained at around 95
8 percent and mean difference decreased to 0.03 diopters per
9 month.

10 At the time of my written review, analysis of the
11 9 months consistent cohort were based on a rather small n.
12 Sponsor has submitted stability analysis based on an updated
13 9 months consistent cohort of 131. It is important to
14 consider these outcomes in assessing the appropriate
15 stability endpoint for each of the three indications.

16 This slide presents analysis of the updated 9
17 months consistent spherical cohort comprised of 61 eyes. As
18 you can see, between 1 and 3 months, 96.7 percent of the
19 eyes had a change in MRSE less than or equal to 1 diopter.
20 There was a mean difference of 0.04 diopters, or 0.02
21 diopters per month.

22 All key safety and efficacy outcomes for spherical
23 cohort met and/or surpassed the recommended target values in
24 myopic guidance at 3 months and beyond. There was an
25 improvement in all outcomes between 6 and 9 months exams.

1 Between 3 and 6 months, however, there was a slight decrease
2 in MRSE plus or minus half diopter from 68.5 to 64 percent.
3 All other outcomes remained the same or improved between 3
4 and 6 months.

5 With regard to the above findings, the panel is
6 asked to consider whether 3 or 6 months is the appropriate
7 time point for the safety and effectiveness analysis of the
8 spherical cohort. If 6 months is the appropriate endpoint,
9 does additional 9 months data on the spherical cohort need
10 to be submitted to FDA prior to approval?

11 Sponsor has provided in their submission key
12 safety and efficacy outcomes stratified by diopter at both 3
13 and 6 months. While accuracy of MRSE within half a diopter
14 exceeds 50 percent for all other preoperative dioptric
15 strata of spherical hyperopic cohort, outcomes for the eyes
16 with preoperative MRSE of +5.00 to +6.00 diopters are 40
17 percent at 3 months and decreased to 30 percent at 6 months.
18 Likewise, at 3 months eyes with preoperative MRSE +5.00 to
19 +6.00 as the only dioptric strata was accuracy of MRSE
20 within plus 1 diopter below 75 percent, and this percentage
21 is further reduced at 6 months.

22 UCVA in all the safety outcomes are acceptable at
23 3 months for these eyes. At 6 months there is a loss of two
24 lines of BSCVA for this group of 10 percent. This
25 percentage, however, is based on only one eye, and that

1 cannot be given much weight.

2 In light of decreased accuracy of MRSE for eyes
3 with preoperative MRSE +5.00 to +6.00 diopters, panel will
4 be asked whether approval for treatment of spherical
5 hyperopes should be limited to +5.00 diopter spherical
6 equivalent.

7 Now let's look at stability of hyperopic
8 astigmatism cohort. Percentage of eyes in the 6 months
9 consistent hyperopic astigmatism cohort within 1 diopter
10 MRSE remained constant at 95.8 percent between 1 and 3 and 3
11 and 6 months. The mean difference decreased from 0.14
12 diopters, or 0.07 diopters per month, between 1 and 3 months
13 to 0.06 diopters, or 0.02 diopters per month, between 3 and
14 6 months.

15 Updated 9 months consistent hyperopic astigmatism
16 cohort has 50 eyes. Between 1 and 3 months, 98 percent of
17 the eyes had a change in MRSE less than or equal to 1
18 diopter, with a mean difference of 0.05 diopters, or 0.025
19 diopters per month. Between 3 and 6 months, 94 percent of
20 this cohort had a change in MRSE within 1 diopter, with a
21 mean difference of 0.01 diopter.

22 Key safety and efficacy outcomes for hyperopic
23 astigmatism cohort remain the same or had an improvement
24 between 3 and 6 months, with the exception of accuracy of
25 MRSE within plus or minus half diopter, which decreased from

1 64.7 percent at 3 months to 56.3 percent at 6 months. In
2 light of stability analysis and the decrease in accuracy of
3 MRSE between 3 and 6 months, the panel is asked to consider
4 whether 3 or 6 months is appropriate time point for the
5 safety and effectiveness analysis of hyperopic astigmatism
6 cohort.

7 Sponsor was requested to stratify outcomes by
8 diopter of preoperative MRSE for all indications.
9 Stratification of hyperopic astigmatism data are presented
10 here. While accuracy of MRSE within half and 1 diopter
11 appears to dip for the 4 to 4.99 diopter group, it improves
12 for the 5 to 6 diopter group. Likewise, UCVA outcomes do
13 not appear to decrease progressively with increase in preop
14 MRSE. There were no losses of BSCVA greater than two lines
15 for any group, and BSCVA loss of two lines did not increase
16 significantly with increase in preoperative MRSE.

17 Six months stratified analysis reveals a rather
18 similar picture with the exception of somewhat high losses
19 of two lines of BSCVA for eyes with preoperative MRSE
20 greater than 4 diopters. One must keep in mind, however,
21 how small the denominator is for each of these subgroups.

22 The panel is asked to consider these outcomes in
23 their deliberations on the appropriate range for approval of
24 hyperopic astigmatism treatment.

25 The file currently does not contain stratification

1 by baseline cylinder of key safety and efficacy outcomes for
2 hyperopic astigmatism cohort. The file does, however,
3 contain information on availability of hyperopic astigmatism
4 eyes stratified by baseline cylinder.

5 At 3 months, there are eight eyes with baseline
6 cylinders 3 to 3.9 diopters, three eyes with baseline
7 cylinder 4 to 4.9, and six eyes with 5 to 6 diopters. At 6
8 months, these numbers are as following: six eyes with
9 baseline cylinder 3 to 3.9, three eyes with baseline
10 cylinder 4 to 4.9, and five eyes with 5 to 6.

11 Panel members are asked to take this information
12 into consideration as well as outcomes stratified by
13 preoperative MRSE when considering the appropriate
14 refractive range for approval of hyperopic astigmatism
15 treatment.

16 As mentioned previously, the study was not
17 originally designed for evaluation of three indications;
18 rather, astigmatic cohort was stratified into hyperopic
19 astigmatism and mixed astigmatism cohort at the request of
20 FDA. Currently, mixed astigmatism cohort has 61 eyes at 3
21 months, 43 eyes at 6 months, and 7 eyes at 9 months. Panel
22 members are asked to comment on the adequacy of the sample
23 size of the mixed astigmatism cohort for the purposes of
24 determining safety and effectiveness.

25 In my written review, I have pointed out that eyes

1 with mixed astigmatism are expected to have MRSE close to 0,
2 both pre- and postoperatively. Thus, in my opinion,
3 analysis of stability for mixed astigmatism cohort based on
4 change in MRSE less or equal to 1 diopter is essentially
5 meaningless. Sponsor has performed analysis of stability of
6 the manifest refraction cylinder for this group. One
7 hundred percent of eyes in the 6 months consistent mixed
8 astigmatism cohort had a change of less than 1 diopter in
9 manifest refractive cylinder between 1 and 3 and 3 and 6
10 months. Mean difference of the manifest refraction cylinder
11 was 0.015 diopters per month between 1 and 3 and 0.013
12 diopters per month between 3 and 6 in the 6 months
13 consistent mixed astigmatism cohort.

14 Analysis of the manifest refraction cylinder for
15 the updated 9 months consistent cohort is presented on this
16 slide. Panel members are asked to consider whether analysis
17 of the stability of the manifest refraction cylinder
18 adequately establishes overall stability of the mixed
19 astigmatism cohort.

20 Since typical stratification by preoperative MRSE
21 is of little significance for mixed astigmatism cohort, the
22 sponsor was requested to perform an additional analysis of
23 the effect of asymmetry between the myopic and hyperopic
24 axis. Specifically, the sponsor was requested for
25 stratified outcomes in 1 diopter increments of the

1 difference between the absolute magnitudes of the ablations
2 in the two meridians. Sponsor has performed an analysis
3 requested by FDA and submitted in an amendment dated 2/21.
4 The panel is asked to make a recommendation regarding the
5 most appropriate stratification of key safety and efficacy
6 outcomes for mixed astigmatism indication. Panel members
7 are also asked for recommendation on any additional
8 analysis, if any, they feel are appropriate for evaluation
9 of the mixed astigmatism cohort.

10 The postoperative self-evaluation performed in the
11 study was collected postoperatively with a majority of eyes
12 at 6 months and the remaining eyes at 3 months or later.
13 Data submitted originally combined all presentation of
14 symptoms at 3 months or later. In my review, I raised the
15 question regarding the necessity of stratification of
16 patient questionnaire outcomes by the various time points.
17 In response to my review, sponsor has submitted patient
18 symptoms for the overall cohort stratified by the various
19 time points. Panel members are asked to consider whether
20 the sponsor should be requested to resubmit the patient
21 questionnaire outcomes stratified by the various time points
22 for each of the three cohorts.

23 This concludes my brief comments, and I will now
24 restate the questions for panel consideration.

25 Question No. 1: What is the appropriate stability

1 time point, 3 or 6 months, for the safety and effectiveness
2 analysis of the spherical cohort? If 6 months is the
3 appropriate endpoint, does additional 9 months data on the
4 spherical cohort need to be submitted to FDA prior to
5 approval?

6 Should approval be limited to +5.00 diopter
7 spherical equivalent for the treatment of spherical
8 hyperopes?

9 Question No. 2: What is the appropriate stability
10 time point for the safety and effectiveness analysis of the
11 hyperopic astigmatism cohort? Is addition 9 months data
12 needed prior to approval? Is approval recommended for the
13 full refractive range of the hyperopic astigmatism, i.e., up
14 to +6.00 diopter sphere and up to -6.00 diopter cylinder?

15 Question No. 3: Is the sample size of the mixed
16 astigmatism cohort adequate for the purposes of determining
17 safety and effectiveness? Does stability of the manifest
18 refraction cylinder adequately establish overall stability
19 for this cohort? If not, what additional stability analyses
20 are needed?

21 What is the most appropriate stratification of key
22 safety and efficacy outcomes for mixed astigmatism cohort?
23 What additional analysis, if any, does the panel recommend
24 for evaluation of the mixed astigmatism cohort?

25 Question No. 4: Is the presentation of patient

1 symptoms at 3 months or later sufficient or should the
2 sponsor be requested to resubmit the patient questionnaire
3 outcomes stratified by the various time points for each of
4 the cohorts?

5 And, finally, Question No. 5: Are there any
6 additional labeling recommendations?

7 This concludes my presentation. Thank you for
8 your attention.

9 CHAIRMAN McCULLEY: Could we have the lights back
10 on?

11 So FDA has nothing further to present at this
12 time. Okay. Panel questions for FDA, and then at the
13 conclusion of our asking our questions to the full extent
14 that we wish, we will give sponsor the opportunity
15 succinctly to make additional comments or clarifications?
16 So at this point, Marian?

17 DR. MACSAI: Malvina, excellent presentation, as
18 always.

19 DR. EYDELMAN: Thank you.

20 DR. MACSAI: In one of the reviews, the question
21 was raised of what's an appropriate n to demonstrate safety
22 and efficacy, especially regards to mixed astigmatism? I
23 think the question was raised by Dr. Grimmert in his review,
24 and I was wondering if the agency's statisticians could
25 provide us with that because it would help answer the last

1 part of your questions.

2 DR. EYDELMAN: Well, we have an n for new
3 indication, and that has been somewhere in the range of 125
4 to 150 eyes. But we bring the question of mixed astigmatism
5 for your consideration in light of--twofold, actually, in
6 light of the fact that, A, it's a new subcategory, which we
7 determined is a new indication; and, second, in light of the
8 somewhat smaller population basis in U.S. and also in light
9 of this particular application and how the ablation is
10 performed. Sponsor tried to demonstrate that in their
11 opinion the ablation is similar, and we wanted your advice
12 on the appropriate size of the cohort, combining all of
13 those factors. And if you point to what it is you want us
14 to base the statistical analysis on, we'll be happy to
15 perform it.

16 CHAIRMAN McCULLEY: Arthur?

17 DR. BRADLEY: The FDA asked the sponsor to divide
18 up the data based upon whether they were mixed astigmats or
19 hyperopic astigmats. Could you give us some indication of
20 the rationale for that? Is there some belief that there's
21 something fundamentally different about either the procedure
22 or the underlying biology of these corneas? What was the
23 motivation for this stratification?

24 MS. HOANG: The reason for our request was based
25 on the pattern that is ablated on the eye. We feel that the

1 correction for hyperopic astigmatism versus mixed
2 astigmatism involves different patterns and, therefore, we
3 would like to know if those patterns somehow would affect
4 outcomes. That's why we asked the two to be broken out.

5 CHAIRMAN McCULLEY: Dr. Maguire?

6 DR. MAGUIRE: Was another reason that it was asked
7 to be broken up because there will be other applications
8 from other companies that used a different methodology to
9 attain the same result, and these, because they use
10 different methods of ablation, might have more trouble with
11 centration and so on, you want to have comparable groups
12 between applications? Did that factor in at all?

13 MS. HOANG: With respect to this application, as
14 with any application, if there are different patterns being
15 ablated on the eye, we would like to see the effect of each
16 pattern.

17 DR. MAGUIRE: Okay. I think--

18 DR. ROSENTHAL: This is Dr. Rosenthal. The
19 decision was based upon the profile and solely upon the
20 profile. The method by which different companies achieve
21 different results are also taken into consideration if the
22 profiles are different.

23 DR. MAGUIRE: Okay. And a second quick question.
24 Can the FDA statistical people comment on the importance of
25 statistical power in evaluating whether a statistically

1 significant difference is present or not when you have a
2 small number of people in a group? Because there are times
3 where when people find a lack of a statistically significant
4 difference between groups, it doesn't mean anything, if you
5 don't have enough people in the groups to discover
6 statistically significant differences.

7 CHAIRMAN McCULLEY: Identify yourself.

8 DR. LU: T.C. Lu, Biostatistics. Of course, the
9 power is important in determining the sample size for the
10 trial, yes.

11 DR. MAGUIRE: Okay. And would you consider that
12 the number of people in the higher ranges of hyperopia in
13 this submission are of adequate sample size to discover a
14 statistically significant difference if it was there?

15 DR. LU: Well, we have to know the difference to
16 be detected for the higher size. In this moment we don't
17 know what the sponsor wants to be determined, the difference
18 to determine the sample size.

19 CHAIRMAN McCULLEY: Arthur?

20 DR. BRADLEY: Back to the stratification of mixed
21 versus hyperopic astigmats. You've given us the rationale
22 for why we did that originally. Could you give us a summary
23 conclusion? Did you find significant differences between
24 these two groups, or could they be grouped together as a
25 single group?

1 DR. EYDELMAN: As you could see, the data is
2 presented for your consideration, and we're interested in
3 your opinion at this point.

4 CHAIRMAN McCULLEY: From a clinical standpoint,
5 the rock and hard place that we've been caught between as we
6 have myopic and myopic astigmatic correction, then if we
7 have hyperopic and hyperopic astigmatic correction, mixed
8 kind of gets lots in the shuffle. And whether it's, you
9 know, anything different or just applications of the same
10 thing in a different way might be the point that one could
11 debate. And I suppose it depends on how each laser treats
12 it--again, what the technology application is to create the
13 pattern if the patterns are very different. And I haven't
14 analyzed carefully the difference between the patterns in
15 myopic astigmatism and hyperopic astigmatism, but what
16 you're saying is that mixed astigmatism is done with a very
17 different pattern. And if that's true, then I see your
18 rationale for having the company, you know, have it as a
19 separate--you'll get a chance, sponsor.

20 But, anyway, I'm not sure how important this is to
21 our deliberations. It's been done and we have the
22 stratification. Go ahead.

23 DR. BRADLEY: The reason I'm asking this follow-up
24 question, I was looking for a lead answer from the FDA, is
25 that you've posed us the question of whether there are

1 significant sample sizes in these groups after
2 stratification into mixed and hyperopic astigmats. So the
3 question is: Can we group them together? If we can, then
4 we have larger n's in these high astigmatic groups. And
5 then this whole statistical question changes. That's why
6 I'm asking--

7 DR. ROSENTHAL: If you group them together, you
8 have to group them together based upon the rationale
9 because, as Dr. McCulley pointed out, different lasers will
10 do them different ways. And the rationale for one laser may
11 not be the same for the other laser.

12 DR. BRADLEY: But we're only considering one
13 laser.

14 DR. ROSENTHAL: Correct, but I want--but I would
15 appreciate, if you do decide to lump rather than split, you
16 explain why so that future sponsors will not come in and say
17 you allowed them to lump, we want to lump. So you
18 understand what--

19 CHAIRMAN McCULLEY: Well, I'm surprised that they
20 were able to enter those patients in the study because they
21 represent a different clinical population. I think it's
22 great that they did.

23 DR. ROSENTHAL: Well, you have to look at the
24 indication, Dr. McCulley.

25 CHAIRMAN McCULLEY: Well, I know. There was a

1 little loophole there, and it apparently caught you by
2 surprise, too.

3 [Laughter.]

4 CHAIRMAN McCULLEY: Other questions--

5 DR. ROSENTHAL: I don't think it was done
6 intentionally. They decided to study, whatever it was,
7 +6.00 with a -6.00 cyl, and because they treat minus in a
8 minus way for everybody, they're going to include people who
9 will be minus in one meridian, plus in another meridian.

10 CHAIRMAN McCULLEY: Oh, I understand how it came
11 about. We've got a lot of mixed astigmats out there
12 flapping in the breeze.

13 DR. ROSENTHAL: Excuse me. I think that should be
14 part of your deliberation about the issues relating to mixed
15 astigmatism.

16 CHAIRMAN McCULLEY: Yes. I mean, if this were all
17 just a statistical consideration, then you wouldn't need a
18 panel.

19 DR. ROSENTHAL: We always need a panel.

20 CHAIRMAN McCULLEY: Of course.

21 Other questions for FDA?

22 [No response.]

23 CHAIRMAN McCULLEY: Okay. In closing this
24 session, and before we break for lunch, after which we will
25 have the primary reviews, I'd like to ask sponsor if they

1 wish to make additional comments directed at the discussions
2 that we've just had with the FDA or their presentation or if
3 there are points of clarification relative to that. It's
4 not an opportunity to make another presentation or bring up
5 different issues, but do you have comments related to these
6 discussions?

7 DR. GAUTHIER: I'm Charlene Gauthier from
8 Autonomous, and I'd just like to answer some of the
9 questions that came up previously. Dr. Matoba and Dr.
10 Grimmett or Dr. Macsai asked some questions that we didn't
11 have the immediate answer to.

12 Dr. Matoba, you had asked about the eyes that had
13 lost two lines of best corrected vision in the hyperopic
14 astigmat group. It's 5.5 percent at 3 months, 6.9 percent
15 at 6 months, and it was 8.8 percent at 9 months. That
16 represented seven eyes at 3 months, seven eyes at 6 months,
17 and five eyes at 9 months.

18 The answer to the question about the group with
19 cylinder of 3 to 3.99, are they different or special? Many
20 of these eyes--there were 19 preoperatively. Five of them
21 had a sphere of 5 to 6 diopters. Six of them had a sphere
22 of 0 to 1 diopter. And then the remainder, there were two
23 or three in each other diopter group, but a preponderance of
24 the high cylinder and the low cylinders, when we look at
25 those that are undercorrected, the five that were from 5 to

1 5.99 were all under--sorry, overcorrected more than a half
2 or 1 diopter. So they're the ones that really dropped the
3 percentages, as well as the group in the 0 to 0.99 group, of
4 the six preop, four of them also fell outside of that range.
5 So those eyes in the two extremes of the sphere population
6 are really the ones that were out of range.

7 CHAIRMAN McCULLEY: Dr. Macsai?

8 DR. MACSAI: Are we allowed to ask questions now
9 or not?

10 CHAIRMAN McCULLEY: If they're pointed.

11 DR. MACSAI: Well, it's very pointed. Did you
12 adjust or are you adjusting your nomogram so you don't
13 overcorrect these people with the 5 to 6 and 0 to 0.99
14 sphere with cyl that fall into 3 to 3.99? Because it's got
15 to be a nomogram that causes them to be overcorrected.

16 DR. GAUTHIER: I think that that's an excellent
17 point, and certainly what we found in our initial approval
18 is when the system is out in doctors' hands, there's not
19 only some nomogram adjustment for people on the extents of
20 the range, but also for their own technique, humidity, room
21 environment, et cetera. And I believe that that's the case
22 here, that they will--we will need to advise on some
23 adjustment for those low--

24 CHAIRMAN McCULLEY: Okay. We don't want broad
25 discussions here. I think we want questions--your response,

1 and then we'll decide about questions. But I think that
2 gets potentially--my fault. We got off on--that's probably
3 thin ice. So if you would continue.

4 DR. GAUTHIER: My final comment is with regard to
5 the labeling. The labeling provided to you is really--the
6 format is based on the approved labeling that we currently
7 have, and we certainly realize and are very willing to
8 accept the labeling recommendations of the panel to modify
9 that in any way. But the template we used was our current
10 approved labeling which had been reviewed by FDA for our
11 first approval. So those issues that aren't recognized in
12 this labeling like the cylinder one or the worse symptoms,
13 we're absolutely willing to put those in, just so you have
14 some background on why they're not there.

15 CHAIRMAN McCULLEY: Further comments?

16 DR. PETTIT: Just really quickly. In my earlier
17 presentation, I was attempting to show the shot patterns and
18 how there really is a continuum of all types of corrections.
19 And if you just remember back, the mixed astigmatism was
20 sort of right in the middle of all of the examples that I
21 gave. So it really does sort of straddle myopic astigmatism
22 versus hyperopic astigmatism, and it's just part of that
23 overall continuum. I just wanted to make sure that was
24 clear.

25 CHAIRMAN McCULLEY: So you don't think it's so

1 terribly different?

2 DR. PETTIT: No.

3 DR. MAGUIRE: Just a comment--

4 CHAIRMAN McCULLEY: Well, do you have any--does
5 that conclude your comments?

6 DR. GAUTHIER: Yes, it does. Thank you.

7 CHAIRMAN McCULLEY: Not a time for comments

8 DR. MAGUIRE: Okay.

9 CHAIRMAN McCULLEY: If there is a pointed question
10 to their clarifications, that's allowable.

11 DR. ROSENTHAL: I'd like to make a comment,
12 though, if I may.

13 CHAIRMAN McCULLEY: You're allowed.

14 [Laughter.]

15 DR. ROSENTHAL: The sponsor had originally argued
16 that there was a continuum from myopia to hyperopia, that
17 this application was submitted as a continuum. And the
18 agency felt because the myopic part had already been
19 considered under several things that it would not allow an
20 expedited review. The expedited review was given because of
21 the hyperopic part of the thing. So the sponsor agreed to
22 drop the myopic part, which we are reviewing separately for
23 LASIK. Myopic--

24 CHAIRMAN McCULLEY: You're reviewing that in-
25 house?

1 DR. ROSENTHAL: That's correct. So I think you
2 should realize that they have always made the argument that
3 this is a continuum, and we'd appreciate the panel's opinion
4 whether they agree with that argument.

5 CHAIRMAN McCULLEY: Right. We're advisory to you.
6 Dr. Maguire?

7 DR. MAGUIRE: Sorry to keep it going, but just one
8 short comment. It's a continuum--we have a continuum, but
9 we also have an unexpected finding on the most simple
10 portion, the ablation of that continuum. We have a
11 significant number of people with induced cylinder in the
12 simple hyperopic portion of your group. And so it's
13 reasonable to ask if we see an aberration that's unexpected
14 in one part of that continuum, how do those aberrations
15 change as you change along that spectrum of the continuum?
16 And I hope to also look at that in the myopia group
17 separately.

18 CHAIRMAN McCULLEY: Dr. Matoba, you had--

19 DR. MATOBA: Yes. I appreciate that data on the
20 9-month--on the numbers for the percentage of patients in
21 the hyperopic astigmatic group that lost two lines of
22 vision. That means that they go from 5.5 at 3 months to 6.9
23 at 6 months to 8.45 percent at 9 months. So although the
24 numbers are small, there's an apparent upward trend over
25 time which is different from the other groups. So I

1 wondered if you had any more information about that
2 subgroup, whether they were 20/10 to begin with, or any
3 other thoughts as to why this might be the case.

4 DR. GAUTHIER: The fact that there is nobody worse
5 than 20/32 suggests that they're at least 20/20, and some of
6 them are probably better than 20/20. We can, again, further
7 delve into that and give you that answer on the individual
8 eye, but I don't have it right here.

9 CHAIRMAN McCULLEY: Okay. Let me clarify
10 something. I think in terms of what--we potentially have
11 opened up a can of worms here. If there are specific
12 comments or questions relative to the issues that sponsor
13 brought back to the table, I think further comment is okay.
14 For us to introduce clarification or request clarification
15 on anything else is not appropriate. I know, yours was.
16 You did fine. I just wanted to make sure that any further
17 comments were within those parameters. Yours was.

18 Dr. Pulido?

19 DR. PULIDO: It does, if I phrase it properly.
20 Sponsor has been very kind to submit a logistic regression
21 analysis looking at variables associated with ultimate
22 outcomes. Considering what has been discussed, how are you
23 taking the results of this logistic regression analysis into
24 consideration in the future use of your--for future use in
25 astigmats?

1 DR. GAUTHIER: I'm not sure I understand.

2 CHAIRMAN McCULLEY: Must not be within what they
3 were talking about, Jose. Can you rephrase it? Maybe not
4 trying to stay politically correct, since you already have
5 the floor.

6 DR. PULIDO: You have provided a very nice
7 statistical analysis starting on Section A.4. How is that
8 going to change what you do for future nomograms, et cetera,
9 if any? Or are you going to totally discard this data?

10 DR. GAUTHIER: No. No, we're not going to discard
11 the data. George would like to speak to it.

12 DR. PETTIT: Well, I don't want to, but I will.

13 We collect all the data we can on every patient,
14 and we will have that data in the same type of format you
15 saw available to future clinical users of the device. But I
16 think we'd have to work with the agency as far as what
17 changes we could actually implement versus what kind of
18 guidance we can give in labeling or education. I'm not sure
19 exactly how that will work.

20 DR. PULIDO: Because there is a significant
21 difference between persons who are 30 to 39--well, there was
22 too few--40 to 49, 20/20 or better uncorrected visual acuity
23 was 75 percent versus greater than 60, only 21.9 percent.
24 Significant.

25 DR. GAUTHIER: Yes, I think, again, in terms of

1 how any kind of nomogram issues are displayed to the
2 practitioner is something that we need to work with FDA on
3 how they want us to present that, whether in training or
4 labeling. But we definitely will use the information.

5 DR. ROSENTHAL: I think we're on a new topic.

6 CHAIRMAN McCULLEY: I do, too.

7 DR. ROSENTHAL: That is, the relationship between
8 age and results, if I'm not mistaken.

9 CHAIRMAN McCULLEY: We have to be careful about
10 what we do and how we do it because of the consideration of
11 setting precedents and the like. And sponsor, I gathered,
12 really wanted this opportunity. You have to be kind of
13 careful what you ask for. You might get it. But I think we
14 do need to try to stay within some bounds.

15 Thank you for your comments, and at this point it
16 is 12:30, roughly. Sally is going to make a comment before
17 we break for lunch, and then we're going to have a one-hour
18 break for lunch. Sally?

19 MS. THORNTON: I just wanted to mention to the
20 panel that the lunch area for us is Room 20-H, right out
21 here and down the hall a bit. And we'll meet you back in an
22 hour.

23 [Luncheon recess.]

1 the study population, safety issues, efficacy issues, and
2 then the treatment range.

3 Regarding the study population, as has been
4 previously indicated, it was primarily a Caucasian cohort.
5 The labeling should reflect this, and outcomes in other
6 groups are unknown. The average age in this population was
7 53 years old. Using Donder's (ph) table, there may be a 2
8 diopter residual accommodative reserve at that age range.
9 Thirty-one percent were less than 50; hence, some patients
10 in this cohort may have sufficient accommodative reserve to
11 overcome low levels of hyperopia and possibly skew some of
12 the outcomes. I'll give two examples: 15 percent of
13 cyclopleged eyes, for example, were undercorrected greater
14 than a diopter at 6 months while 8.6 percent of non-
15 cyclopleged eyes were undercorrected greater than a diopter
16 at 6 months.

17 Regarding the uncorrected visual acuity outcomes,
18 there is some evidence to say that accommodative reserve
19 plays a role; however, mydriasis may also play a role in
20 visual aberrations.

21 Overall, manifest versus cycloplegic refraction
22 data were similar at 6 months, indicating that the
23 refraction data are not unreasonably skewed by residual
24 accommodation.

25 In the original submission, the number of eyes

1 available for refractive analysis was sufficient to 6
2 months. There were only 46 eyes available at 9 months.
3 Hence, for the original document, the 9-month data may not
4 be representative of the entire cohort, especially when
5 stratifying into refractive subgroups. The sponsor did
6 provide updated numbers. They appeared too late to be
7 included in my primary review. And while I've considered
8 them today, I haven't had the opportunity for careful
9 review.

10 As far as preop best spectacle corrected visual
11 acuity, 46 eyes were not correctable to 20/20. We speculate
12 that refractive amblyopia may be the culprit in at least
13 some of these eyes.

14 As far as safety issues are concerned, I want to
15 start with subjective symptoms. Several of these symptoms
16 had a fairly high frequency in my book. Light sensitivity
17 and dryness were worse or significantly worse in one of
18 four. Glare, halos, and visual fluctuation were worse or
19 significantly worse in one of five. Blurring of vision,
20 difficulty night driving, worse or significantly worse in
21 one of seven. These taken together would indicate that
22 optical quality has been altered in at least some of the
23 subjects.

24 Overall, one in 18 patients rated their quality of
25 vision or significantly worse following the procedure, and

1 one in eight were either unsatisfied or extremely
2 unsatisfied following the procedure. Hence, based on these,
3 a few labeling recommendations.

4 As has already been discussed, the patient
5 information booklet on page 19 and the physician booklet on
6 page 11 only list the significantly worse category. Since
7 the worse category can be reasonably construed to be a
8 material fact necessary for a given patient to make an
9 informed judgment whether or not to undergo the procedure,
10 the labeling should include both the worse and significant
11 worse symptom category, both to satisfy legal standards as
12 well as the ethical principle of respect for persons.

13 Another labeling recommendation. I was unable to
14 locate satisfaction or dissatisfaction data in the patient
15 information booklet. The approximate one in eight rate of
16 patients unsatisfied or extremely unsatisfied requires a
17 statement to satisfy informed consent standards. Similarly,
18 the quality of vision one in 18 rate worse or significantly
19 worse requires a statement.

20 I was concerned about the one in four rate of
21 dryness. I didn't read every single word, but I would
22 believe that it warrants a precautionary statement in the
23 labeling, if not already done.

24 The study did not evaluate a postop tear
25 deficiency state, things like fluorescein break-up time,

1 rose bengal staining, or Schirmer's tear wetting, although I
2 found it interesting at one month or later, 45 eyes had
3 superficial punctate keratitis, possibly indicative of
4 aqueous tear deficiency, neurotrophic keratopathy, or other
5 etiology.

6 Regarding best spectacle corrected visual acuity,
7 overall at 6 months 4.1 percent lost greater than two lines
8 of best corrected visual acuity--I should say greater than
9 or equal to two lines. I'm considering a two-line loss as
10 clinically meaningful. All eyes were better than 20/40.
11 While not insignificant, this rate likely meets the standard
12 of reasonable safety if we're considering the cohort as a
13 whole without stratifying the data into manifest refractive
14 spherical equivalent ranges.

15 When we stratify the data, we see some different
16 findings if we're stratifying by manifest refraction
17 spherical equivalent. At 6 months, the hyperopic
18 astigmatism subgroup has a high 17.6 percent rate of best
19 corrected spectacle visual acuity loss greater than or equal
20 to two lines in the 4.00 to 4.99 diopter range. The 5.00 to
21 6.00 diopter range had a 14.3 percent rate of best corrected
22 visual loss greater than or equal to two lines. And the
23 1.00 to 1.99 diopter range had an 11.5 percent rate of loss.

24 The spherical hyperopia group had a 10 percent
25 rate of loss greater than or equal to two lines in the 5.00

1 to 6.00 diopter range at 6 months.

2 We've all discussed this. The small number of
3 eyes within each stratified subgroup does limit firm
4 conclusions regarding best spectacle corrected visual acuity
5 loss one way or the other, and I don't believe statistical
6 power analysis would say that one way or another we could
7 make firm conclusions.

8 Intuitively, we may expect a potentially higher
9 rate of irregular astigmatism, that is, decreased best
10 corrected visual acuity with higher attempted corrections
11 both for sphere and cylinder. And while the sponsor has
12 nicely provided additional tables for best corrected visual
13 acuity loss stratified solely by the spherical component of
14 the refraction and the cylinder component of the refraction,
15 in my opinion these stratification methods do not precisely
16 describe the totality of refractive ablation for most eyes.
17 So I think part of the panel discussion today will be how to
18 exactly stratify the data when astigmatism is involved so we
19 can make reasonable conclusions regarding safety.

20 Options to deal with the best corrected visual
21 acuity loss findings include limiting the indication for
22 treatment for the higher attempted corrections and/or, at a
23 minimum, mandating postmarketing surveillance with
24 sufficient follow-up and sufficient number of eyes in order
25 to better determine the rate of best corrected visual acuity

1 loss greater than or equal to two lines for the differing
2 spherical equivalent ranges.

3 A labeling recommendation regarding the best
4 corrected visual acuity, page 18 of the "Patient Information
5 Booklet" states, "Other events that did not occur in this
6 study...include significant corneal haze and loss of best
7 corrected visual acuity." Since 11 eyes in this study lost
8 greater than or equal to two lines of best corrected visual
9 acuity at 6 months, this statement appears inaccurate and
10 misleading and requires revision.

11 Regarding induction of cylinder, the spherical
12 hyperopia group--and the comments of Dr. Maguire need to be
13 taken into account. In the spherical hyperopia group, 11
14 out of 125, or 8.8 percent, with greater than or equal to 1
15 diopter of induced cylinder at 6 months, and I'd recommend
16 for informed consent standards putting that information in
17 the labeling other than just the greater than 2-diopter
18 threshold.

19 The third part regarding efficacy issues,
20 regarding stability, I would just make a comment that
21 labeling should reflect the updated stability data that was
22 presented.

23 Regarding predictability, we have seen, at least
24 in the data, that the attempted versus achieved scatterplots
25 show a trend toward undercorrection for spherical equivalent

1 ranges greater than approximately 3 to 4 diopters. And for
2 the cohort as a whole, if you entered the study with a preop
3 spherical equivalent greater than 4 diopters, you don't
4 achieve the FDA target value of 50 percent for plus or minus
5 a half of intended. And a spherical equivalent greater than
6 preop does not achieve the FDA target value of 75 percent
7 for plus or minus 1 diopter of intended.

8 For the spherical hyperopia group, in particular,
9 the percent remaining within plus or minus a half of
10 intended in the 5 to 6 diopter subgroup declines over the
11 study period. Similarly, for the astigmatic hyperopic
12 group, the percent remaining plus or minus a half of
13 intended in the 4.00 to 4.99 subgroup declines over the
14 study period.

15 Labeling. At a minimum, appropriate labeling
16 should highlight the declining predictability for preop
17 spherical equivalent levels greater than 4 diopters.

18 Regarding uncorrected visual acuity, if we
19 stratify the data by preop spherical equivalent, those
20 having greater than 3 diopters, the percent with an
21 uncorrected visual acuity of 20/40 or better at 6 months
22 falls slightly lower than the FDA target value of 85
23 percent, and those achieving 20/20 or better declines to
24 about one in five if you start with a preop spherical
25 equivalent greater than 4, and the labeling should reflect

1 these data.

2 Regarding retreatment, the total number of eyes--I
3 believe 14 was the number on the slides today--is really too
4 low to generate firm conclusions regarding retreatment
5 outcomes. Additionally, clinical sub-studies were not
6 performed on these retreated eyes, such as endothelial cell
7 counts, (?) lamp data, and other findings. The length of
8 the follow-up I think was shown at 3 months. That's too
9 short. So retreatment outcome comments really cannot be
10 made with reasonable assurance.

11 Part of the major discussion this afternoon, I
12 believe, will focus on the treatment range. The following
13 seven features argue in favor of limiting the treatment
14 range. Where the exact line is drawn will be decided on
15 panel discussion. Everyone has seen my opinion in the
16 primary review, but the following seven features concern me:

17 Number one, for all eyes, there's declining
18 predictability plus or minus a half of intended for preop
19 spherical equivalent ranges greater than 4 diopters. These
20 do not meet the FDA target value of 50 percent.

21 Number two, for the entire cohort, there's a
22 declining predictability plus or minus 1 diopter of intended
23 if you entered the study with a preop spherical equivalent
24 greater than 5 diopters. This doesn't meet the FDA target
25 value of 75 percent.

1 Number three, for the spherical hyperopia group,
2 there was a high 10 percent rate of best corrected visual
3 acuity loss greater than or equal to two lines if you start
4 the study with a spherical equivalent greater than 5
5 diopters.

6 Number four, for the astigmatic hyperopia group,
7 there was a high 14 to 18 percent rate of best corrected
8 visual acuity loss greater than or equal to two lines if you
9 entered the study with a preop spherical equivalent greater
10 than 4 diopters.

11 Number five, for the spherical hyperopia group,
12 there were progressive declines over the study period in the
13 percent remaining plus or minus a half diopter of intended
14 for preop spherical equivalent greater than 5, that is, at
15 1, 3, and 6 months, the percent remaining plus or minus a
16 half decreased from 50 percent to 40 percent to 30 percent.

17 Number six, for the astigmatic hyperopia group,
18 there were progressive declines over the study period in the
19 percent remaining plus or minus a half diopter of intended
20 if you entered the study with a preop spherical equivalent
21 from 4.00 to 4.99. At 1, 3, and 6 months, those remaining
22 plus or minus a half decreased from 50 percent to 39 percent
23 to 24 percent.

24 And, number seven, there's decreased efficacy for
25 achieving various uncorrected visual acuity levels at higher

1 preop spherical equivalent ranges.

2 Taken together, these features would argue in
3 favor of limiting the treatment for the higher dioptric
4 ranges. The question will be: Where should the line be
5 drawn? In my original review, I drew the line on spherical
6 equivalent, spherical hyperopes at 5 diopters and for
7 astigmatic hyperopes at 4 diopters. But I suppose it
8 depends how we stratify the information, whether we're
9 stratifying the bins based on spherical equivalent, based on
10 cylinder alone, or based on sphere alone. I'll be very
11 interested to hear panel discussion in that regard.

12 At a very minimum, I would encourage postmarket
13 surveillance regarding best corrected visual acuity loss,
14 especially given the indication that there may be something
15 in the 1.00 to 1.99 diopter range in the hyperopic
16 astigmatism group.

17 This concludes my comments for now. Thank you.

18 CHAIRMAN McCULLEY: Are there questions for Mike
19 on his review, keeping in mind we have another reviewer? Or
20 do you want to wait until we have heard both reviews for
21 comments? Okay. Arthur?

22 DR. BRADLEY: Just for the record, the chronology
23 here is that I've read the review provided by the sponsor--I
24 mean, the proposal provided by the sponsor, the review by
25 the FDA. I have written a primary review, which is on

1 record, of the sponsor's proposal. The sponsor has then
2 seen my review and replied to it. And rather than rehash
3 everything in the review, I thought it might be worth just
4 having a look at the sponsor's response to the questions and
5 concerns that I raised in my primary review. So I'm just
6 going to go through those one by one.

7 Generally, I started off with some general
8 concerns about the procedure and one concern about ablation
9 accuracy, and the sponsor notes that for the patient it is
10 the sphere and cylinder that need to be corrected, and these
11 are the primary optical problems that the patient
12 experiences. And my comment related to the fact that the
13 procedure itself did not directly change sphere and
14 cylinder, but was a local ablation procedure. And the
15 comment is that it can introduce higher-order aberrations
16 while correcting the sphere and cylinder.

17 Our only indication of this really is the best
18 spectacle corrected VA and contrast sensitivity or our best
19 corrected visual performance measure. If performance is
20 good, we can assume that the ablated procedure did not
21 introduce significant problems. However, when there's a
22 significant percentage of the patients who lose two lines of
23 visual acuity or some other measure of visual performance,
24 we need a way of identifying the cause of this loss.
25 Knowing the spatial distribution of the optical effects may

1 uncover the source of such a problem, and this provides an
2 opportunity to fix the problem. Currently, we do not have
3 those data.

4 The second general issue I raised was one about
5 how to analyze sphero-cylindrical data, and I talked a
6 little bit about this this morning. And the basic problem
7 is one of compressing a sphero-cylindrical refractive data
8 set down to one dimension, whether it be spherical
9 equivalent, magnitude of the cylinder, or axis of the
10 cylinder.

11 This problem is described by the sponsor, and it's
12 included in Dr. Grimmett's review. And in order to perform
13 statistical analysis on this three-dimensional data set, it
14 is typically compressed to one dimension. This subdivision
15 is unnecessary and produces, as the sponsor describes,
16 spurious equivalences. This type of analysis can also
17 obscure important covariances within the data set, and
18 essentially we lose information by doing this. And, of
19 course, the irony here is rather rich in the sense that the
20 photoablative algorithm must embrace the full three-
21 dimensional nature of the problem. But the final output
22 analysis does not, and basically the ablative algorithm is
23 not encumbered by historical precedents, but the clinical
24 evaluation is.

25 The sponsor, in its reply, noted that the FDA has

1 not required this full three-dimensional analysis of spherocylindrical data, and that's correct. The FDA has not
2 mandated this. But other sponsors have been asked to
3 reanalyze data by panel reviewers to embrace this full
4 three-dimensional nature of the data set.

6 Will it uncover any additional valuable
7 information about the efficacy and/or safety? At this point
8 I don't know because we don't have the data.

9 So moving off of these general concerns, we move
10 into issues about data. I noted that there were 13 percent
11 with 20/25 best corrected VA worse. And the sponsor has
12 replied that, well, this is probably normal in this
13 particular data set or this particular cohort group, that
14 is, the highly hyperopic and astigmatic group, and,
15 therefore, we might expect this to be--might anticipate this
16 to be a normal distribution of visual acuities in this
17 group. And they cited a couple of studies to show that
18 other people had likewise found rather poor visual acuities,
19 best correct. The studies, however, were similar to the one
20 performed by the sponsor here that is related to refractive
21 surgery. And I just wonder whether this is, in fact,
22 reality; that is, hyperopes and those with astigmatism in
23 general do have visual acuities that match the distribution
24 found by the sponsor. I don't know that to be true, but I
25 just wondered that.

1 There was a question of accountability, and that
2 seems to be fixed.

3 I did note that the photoablative procedure for
4 astigmatic correction seems to have reduced efficacy, and
5 there are really two reasons this could happen. One is that
6 there is something special about ablating tissue when trying
7 to correct astigmatic corrections, and I don't think that
8 makes any sense at all. Tissue is tissue. The other
9 possible reason for reduced efficacy in astigmatic
10 correction is there is some error in the judgment of the
11 axis of the astigmatic correction. And as I commented in
12 the primary review, the weak link in this procedure by the
13 sponsor seems to be in the original determination of what
14 they call the 3 and 9 o'clock marks on the cornea. It is
15 those marks that the equipment then uses as references and
16 to track the procedure.

17 The sponsor's answer to this is that the mean
18 astigmatic axis error decreases from 12 to 2 degrees as
19 astigmatic magnitude increases from 0 to 6 diopters. And
20 that response basically confirms that the mean location of
21 the 3 and 9 o'clock markers is pretty close. But it may be
22 eye-to-eye variability in these 3 and 9 o'clock markers that
23 cause reduced efficacy in some eyes. And I think that's
24 something that should be looked at.

25 Again, on questions of efficacy, there was a

1 question about stability, and I had raised the question that
2 we've done comparisons 1 to 3 months and 3 to 6 months. But
3 I was concerned about whether if we had data, why not
4 compare 1 to 9 months and we might get a sense of whether
5 there was a large change. And the sponsor's response to
6 that, looking across all groups, is that from 1 to 9 months
7 the mean change in refractive error is one-tenth of a
8 diopter, and that seems to me to be very stable.

9 The issue of safety. The number of eyes with
10 significant vision loss, and the sponsor replies that--let's
11 see. I have a note here that one in 20 will experience
12 significant vision loss, and the question is: Is that
13 something to be concerned about? Is there some general
14 safety issue here that we should be worried about if one in
15 20 are losing--I think it was two lines of acuity. And a
16 comment, again, really to the sponsor is that a controlled
17 study could have put these numbers in perspective.

18 For example, how many would lose two lines after 3
19 to 6 months without any surgery? And you might have--I
20 don't know this, but you might have one in 20 lose two
21 lines. Anyway, so that one in 20 seems to be a safety
22 issue, but without the control data, I'm not sure quite how
23 to interpret that. And it may be that, in fact, even
24 without a surgical procedure, one in 20 would manifest a
25 two-line loss in acuity.

1 There was an observation that I made that the
2 mixed astigmats end up slightly myopic after the procedure.
3 The hyperopic astigmats end up slightly hyperopic after the
4 procedure. And the result was reiterated in the sponsor's
5 response, but it is not clear why this happens, particularly
6 since the sponsor has argued that it's flying spot procedure
7 essentially treats both groups the same. We had this
8 discussion earlier, and the question really to the sponsor
9 is: Why do we get this difference between those two groups?
10 Why are they mixed--do mixed astigmatics end up with a
11 slightly myopic spherical equivalent? And why do the
12 hyperopic astigmats end up with a slightly hyperopic
13 spherical equivalent?

14 Another question relating to efficacy. I raised
15 the issue that the mean cylinder correction approached about
16 70 percent of full correction. And, of course, we would
17 interpret that intuitively as evidence of an under-
18 correction. It's worth pointing out that it could be an
19 overcorrection. Both under- and overcorrections will result
20 in a non-zero cylinder. Likewise, errors in axis of the
21 correction will also lead to non-zero final cylinders.

22 A point that I raised in the primary review which
23 is worth reiterating because it came up this morning in the
24 sponsor's presentation is that they've developed a metric
25 for cylinder correction success that is scaled by the

1 preoperative magnitude of the astigmatism. The concern I
2 have with that is that, first of all, if I can recall the
3 result, it looked as though in the low astigmatic group the
4 success was quite poor, but as astigmatism became larger,
5 seemingly the procedure improved. But because this is a
6 scaled or normalized metric--actually, the result in
7 astigmatic error climbed with the magnitude of the original
8 astigmatism; that is, people with higher astigmatism started
9 off, ended up with a larger astigmatic error in the end.
10 And so that normalized metric of success of the procedure
11 seemed to be a bit misleading, and particularly, I think, if
12 it ever came to be presented to the patients or the
13 clinicians.

14 And it was clear all along that the sponsor was
15 struggling with the astigmatic data set, and I do reiterate
16 that I think a lot of these problems that I saw in the data
17 analysis stem from an inadequate statistical analysis of
18 this spherocylindrical data set.

19 That's the end of my comments.

20 CHAIRMAN McCULLEY: Questions or comments for the
21 primary reviewers?

22 [No response.]

23 CHAIRMAN McCULLEY: Questions or comments in open
24 discussion relative to the PMA? Marian?

25 DR. MACSAI: There are some issues that haven't

1 been raised I think we need to look at as a panel. I think
2 that the sponsor has done an incredible job of allowing us
3 to look at quite a bit of data and, in doing so, identified
4 but did not address in their presentation a disparity in
5 response of middle-aged women on hormone replacement therapy
6 versus not on hormone replacement therapy.

7 Women on hormone replacement therapy had a 26.2
8 percent chance of being greater or equal to 20/20 while
9 those not on hormone replacement therapy had only a 45
10 percent chance, which is almost a twofold increase.

11 In addition, the sponsor segregated out data at 6
12 months the results for both sphere and cylinder of hyperopic
13 LASIK and stratified the data by age of the patients and, in
14 doing so, identified significant changes in results for
15 patients that are older.

16 For example, if you look at the patients in the
17 sphere--and I'm referring for the sponsor's benefit to
18 Section A.4, page 9 of 20, Table 1. If you look at the
19 sphere corrections, in the 30 to 39 age group it's only an n
20 of one, and there's 100 percent greater or equal to 20/20.
21 But if you look at patients 50 to 59, 54 percent are greater
22 than or equal to 20/20 for the spheres. A similar trend is
23 seen for cyls with patients 30 to 39, n of 21, having 52
24 percent greater or equal to 20/20 when just cylinder is
25 looked at. And when the patients are older, from 50 to 59

1 years old, that drops significantly to 34 percent with an n
2 of 41. So this is an important issue for patients regarding
3 efficacy of the device. The other--I think this is what Dr.
4 Pulido was alluding to in his earlier questions of the
5 sponsor.

6 The other issue I'd like to see raised is that of
7 endothelial cell density. This is the first time I've seen
8 a sponsor separate out such a large group of patients with
9 no contact lens wear. In doing so, they seem to have helped
10 us identify patients whose endothelium might recover after
11 contact lenses are discontinued versus those who have a true
12 change. And if you look at the central endothelial cell
13 density in Table 2, Section A.5, page 4 of 6, patients with
14 no contact lens wear at 3 months had a mean percent change
15 of endothelial cell counts of 0.3 percent and at 6 months
16 it's 3.4 percent. That trend is seen in all three groups
17 that the sponsor has segregated of a significant increase in
18 the endothelial cell mean percent change. That warrants
19 further examination.

20 CHAIRMAN McCULLEY: It's a 3 percent, roughly 3
21 percent increase?

22 DR. MACSAI: Well, from 0.3 percent at 3 months to
23 3.4 percent at 6 months.

24 CHAIRMAN McCULLEY: How meaningful is that when
25 we've accepted that there is a plus/minus 10 percent

1 accuracy of endothelial cell count?

2 DR. MACSAI: Well, I don't know. But there's--
3 throughout each group in some it's going up and in some it's
4 going down, and I think the sponsor needs to address if it's
5 going down, is it going to continue to go down? Or is this
6 just a slice in time? You see an effect at 3 months and
7 it's over or what?

8 CHAIRMAN McCULLEY: I don't know, but we have in
9 the past accepted that the accuracy of endothelial cell
10 count has a 10 percent variability. So a 3 percent change I
11 would have trouble getting excited about.

12 DR. MACSAI: Three percent over 3 months?

13 CHAIRMAN McCULLEY: Well, 3 percent change from
14 any one time point to another. I suppose we could ask for
15 continued follow-up of that. The other--

16 DR. MACSAI: Of those patients.

17 CHAIRMAN McCULLEY: What? Those patients?

18 DR. MACSAI: I think of those already enrolled.

19 CHAIRMAN McCULLEY: Okay. Hold that thought.

20 The other--would you propose in the age and the
21 women, would you--Marian?

22 DR. MACSAI: Sorry. Yes?

23 CHAIRMAN McCULLEY: The issues you brought up with
24 age differences and women on and off hormone replacement
25 therapy, you think those would be labeling issues or they

1 would be limits in age and sex approvable?

2 DR. MACSAI: I would ask the statisticians if 45
3 versus 26 percent is statistically significant.

4 DR. PULIDO: I can answer. That is--I'll go to
5 table--Appendix A of that same section, A.2, and the older
6 age is very statistically associated with a different--with
7 a p of 0.0001.

8 CHAIRMAN McCULLEY: Okay. So I'd go back to--
9 well, my question still holds. Would you propose those as
10 labeling issues, or would you propose those as limits of
11 recommended approvable?

12 DR. ROSENTHAL: Or you can put in precautions or
13 warnings. I mean, there are all kinds--

14 CHAIRMAN McCULLEY: Well, that would come under
15 labeling.

16 DR. ROSENTHAL: Yes.

17 DR. MACSAI: Well, it's got to be in there
18 somewhere. We haven't figured out exactly where.

19 CHAIRMAN McCULLEY: Well, I know. I'm asking
20 where you want to put it. Where do you think it ought to
21 go?

22 DR. MACSAI: It can go in labeling.

23 CHAIRMAN McCULLEY: Labeling.

24 DR. MACSAI: But I also think a table of the
25 results by age should also go in there because of the vast

1 difference in results.

2 CHAIRMAN McCULLEY: Yes, and you'd think that
3 maybe the nomogram could be--or algorithm could be adjusted.
4 But that's for future considerations by industry.

5 Any other questions or comments? Leo? And you're
6 next, Joel.

7 DR. MAGUIRE: Again, I think it's important for
8 the panel to seriously look at the problem of individual
9 variation in refractive stability among this group. I would
10 suggest this be a labeling issue. The sponsors describe a
11 0.1 mean change in refraction. We all know from refractive
12 surgery, though, that you can have a point--you can have a
13 mean postop refraction of zero, but if you have a big
14 standard deviation, you still have big problems.

15 I think there is a potential problem here that
16 needs a closer look by the FDA because on Table 31 on
17 Section A.1, page 41, looking--that's a specific subgroup of
18 people with loss of greater than or equal to two lines of
19 best uncorrected vision and 20/40 or worse at any scheduled
20 visit 1 month or later. If you look at the changes in
21 spherical equivalent, among that group of 55 people--55
22 eyes, 16 of them have a change in refractive error of 0.87
23 diopters or more between some refractive intervals measured.
24 Okay? That's high. That's a lot. And it's lost in the
25 averaging of the information.

1 Obviously, just like we have variation in the
2 amount of induced astigmatism in the simple hyperopic group,
3 we also have significant variations in optical stability as
4 measured by manifest refraction among this group. And that
5 needs an analysis in more depth than has been done so far.

6 And--

7 CHAIRMAN McCULLEY: Leo, what was--go ahead.

8 DR. MAGUIRE: And, again, I respect, I have all
9 due respect for the sponsor and the way that they presented
10 their data is the FDA-mandated way, but, again, as someone
11 who's recognizing in this group that there's a significant
12 amount of individual variation among the subgroups, we need
13 to be sure that we have a patient-friendly labeling process.
14 There's a very complicated set of outcomes here with a lot
15 of variability.

16 CHAIRMAN McCULLEY: It comes under the 1-diopter
17 change from two points 3 months apart, but it's real.

18 DR. MAGUIRE: Many of these people--let's see.
19 Out of that 16--

20 CHAIRMAN McCULLEY: Ninety-five percent are less
21 than one 3 months apart.

22 DR. MAGUIRE: But if you look at individual time
23 slots and compare, okay, over here in this table, there are
24 many people--there are 16 of 55 people in Table 31, Section
25 8.141 that, if you go through and do the math, have 0.87-

1 diopter to 2-diopter change, and there's mean spherical
2 equivalent between points. And what's happening is I think
3 that's getting averaged out in the group.

4 CHAIRMAN McCULLEY: No, you don't--one of the--I
5 may be misunderstanding. One of the stability measures is a
6 mean, and we're averaging it.

7 DR. MAGUIRE: Correct.

8 CHAIRMAN McCULLEY: The other is individual
9 patient, 95 percent of the individuals from one time point
10 to another 3 months apart cannot have a refractive change
11 more than a diopter.

12 DR. MAGUIRE: Well, there's a lot of them here
13 that do on Table--

14 CHAIRMAN McCULLEY: Less than 5 percent.

15 DR. MAGUIRE: No, no. It's 16 of 55 people in
16 this table. I don't know about the whole group.

17 CHAIRMAN McCULLEY: What population is that?

18 DR. MAGUIRE: The table--

19 CHAIRMAN McCULLEY: What does the table represent?

20 DR. MAGUIRE: Key variables for eyes with loss of
21 greater than two lines of best uncorrected vision.

22 CHAIRMAN McCULLEY: Okay. But that's a subgroup
23 of--

24 DR. MAGUIRE: That's right. That's the only group
25 we know about, and we don't know about the other group.

1 CHAIRMAN McCULLEY: We know about the total group.

2 DR. MAGUIRE: No, we don't.

3 CHAIRMAN McCULLEY: Yes, we do. They presented
4 data on the whole group that showed--I don't remember the
5 exact numbers, but it was 95 or greater percent had within
6 1-diopter manifest refraction 3 months apart.

7 Now, if you take a subgroup that's not doing as
8 well, then that's a different kettle of fish. And I think
9 that that may be--you know, it could become a labeling
10 issue. I'm not sure how you take a subgroup that's already
11 done poorly two lines or more loss.

12 DR. MAGUIRE: Well, let me put it this way: I'd
13 like to look at the raw data for the ones that are outside
14 this group to make sure that the information that the
15 sponsor is giving is accurate.

16 CHAIRMAN McCULLEY: Well, I think we have to--

17 DR. MAGUIRE: And that's something that can do--

18 CHAIRMAN McCULLEY: Well, but the FDA has done
19 that.

20 DR. MAGUIRE: I want to clarify that the FDA has.
21 We don't have to deal with it now, but we should deal with
22 it after--

23 CHAIRMAN McCULLEY: Well, I think--

24 DR. PULIDO: A point of clarification. We have to
25 suspect that it is, so you have to go with the idea and

1 belief that that has been--that that is correct data.

2 CHAIRMAN McCULLEY: We enter into this assuming
3 complete honesty and divulgence on the part of the sponsor.
4 FDA monitors sites to ensure that that occurs. The FDA gets
5 the data and they analyze the data, and I don't think we can
6 question their ability, whether they did it effectively or
7 not. That really is not our role. We have to--that's their
8 job. They bring to us the issues that they want our advice
9 on from a scientific standpoint, safety and efficacy.

10 DR. ROSENTHAL: May I just interject? I'm not
11 sure what this is about except that all studies have
12 bioresearch monitoring procedures and investigations,
13 thorough investigations of all sites to ensure--

14 DR. MAGUIRE: Dr. Rosenthal, I respect that and
15 will drop this, and I'll maybe discuss it after with you.

16 DR. ROSENTHAL: Okay. But, I mean, we--

17 DR. MAGUIRE: To make sure we're talking about the
18 same thing.

19 DR. ROSENTHAL: But we will not--but I'd like to
20 just assure the panel that the agency would not bring a PMA
21 to final closure--this isn't final closure--to final closure
22 without assurance that all bioresearch monitoring issues
23 have been--standards have been met.

24 CHAIRMAN McCULLEY: Joel?

25 DR. SUGAR: Just a brief comment on Marian's

1 comment about cell density. The cell densities in general
2 increased and the numbers are small--the changes are small
3 enough as to not be statistically significant. They're less
4 than the variability of the measurements. But the changes
5 are in general towards increasing numbers.

6 CHAIRMAN McCULLEY: Rather than decreasing.

7 DR. SUGAR: With discontinuation of contact lens--

8 DR. MACSAI: I misread the table.

9 DR. SUGAR: Also in the non-lens wearers.

10 DR. MACSAI: I went down instead of across.

11 CHAIRMAN McCULLEY: Marian made a mistake?

12 DR. MACSAI: Oh, it happens all the time.

13 [Laughter.]

14 CHAIRMAN McCULLEY: We're talking about a mental
15 ones. The physical ones, yes. Marian's a famous bike
16 rider.

17 Any other--Arthur?

18 DR. BRADLEY: Just to follow up on Dr. Maguire's
19 comment, it seems to me that he has identified a rather
20 interesting covariance between safety, this subgroup that he
21 was looking at, the ones who did lose two lines of VA, best
22 corrected VA, and efficacy. Within this group, there is
23 this tend to drift. What that means I don't know, but it's
24 certainly worth the sponsor knowing that that covariance is
25 there.

1 DR. ROSENTHAL: We appreciate it, and we will
2 certainly look into the issue. But we have to look at the
3 group pretty much as a totality. The more we start to
4 dissect all these various refractive things, there are
5 always variations in the various things, and we have to--I
6 mean, you know, every applicant so far, nothing is perfect
7 in every single area.

8 DR. BRADLEY: I agree and accept that. I just
9 think it should be clarified before final labeling is--

10 DR. ROSENTHAL: We would certainly clarify, and we
11 appreciate you bringing it to our attention. And it may be
12 something that we will deal with quite strongly in the
13 labeling.

14 CHAIRMAN McCULLEY: Dr. Pulido, you went up, you
15 went down. Do you--

16 DR. PULIDO: I was waiting for my colleagues to
17 stop talking.

18 [Laughter.]

19 DR. PULIDO: Respectfully.

20 CHAIRMAN McCULLEY: Would you speak into the
21 microphone?

22 DR. PULIDO: I would just like the sponsor, again,
23 when they come one more time--they do have one more chance
24 to come and talk--

25 MS. THORNTON: Make final comments.

1 DR. PULIDO: Yes, final comments. To talk about
2 how they are going to incorporate the regression analysis
3 data into their labeling and into future nomograms, the same
4 question I asked this morning.

5 CHAIRMAN McCULLEY: Okay. Was that one that they
6 had trouble understanding what you were getting at? I'm not
7 being a smart aleck now. Or was that one that was
8 understood by sponsor? Understood by sponsor, okay.
9 Otherwise, I was going to make sure that Jose kept going
10 because it's not going to be an interchange when you come
11 back. I think you made your point effectively.

12 Other questions or comments?

13 [No response.]

14 CHAIRMAN McCULLEY: Let me think out loud here
15 with you. As I understand it and think our best process
16 would be, this would conclude in a moment, if we agree, the
17 committee discussions, but then open public hearing, then
18 FDA closing comments, sponsor's closing comments, and all of
19 the issues that have been brought up.

20 DR. SUGAR: What about the questions?

21 CHAIRMAN McCULLEY: Good point. All of the points
22 that have been brought up would be dealt with as conditions,
23 assuming an approvable recommendation. But now, when does
24 the FDA want us to answer, respond to your questions? At
25 this point?

1 MS. NEWMAN: Yes.

2 DR. ROSENTHAL: Yes.

3 CHAIRMAN McCULLEY: Okay. So at this point, can
4 you project your questions? And maybe Quynh can get set up
5 for her little thingamodoo. Quynh is going to--as we get
6 to--what? When we start listing conditions, if we get to
7 listing conditions, Quynh is going to project them, as I
8 understand it. That's when we get down to motions and so
9 forth, but she can be setting up now while Malvina is--are
10 you okay?

11 DR. ROSENTHAL: Yes. Apparently it has been--I
12 didn't know we had to type out these.

13 CHAIRMAN McCULLEY: Yes, that's what I've been
14 told. All right. So now we're going to go through the
15 questions.

16 DR. EYDELMAN: Since we only have one monitor, if
17 I'm projecting the questions, she can't be typing the
18 answers.

19 CHAIRMAN McCULLEY: We're not typing the answers
20 until later. I just wanted to make sure that you had set up
21 what you needed to have set up. So let's go through the FDA
22 questions to us at this point.

23 The first question, do you want to read it to us?

24 DR. EYDELMAN: What is the appropriate stability
25 time point, 3 or 6 months, for the safety and effectiveness

mc

1 analysis of the spherical cohort?

2 CHAIRMAN McCULLEY: Anyone want to--I can give
3 what my impression is, but I think it's probably better if
4 one of you do. Mike, what's your--

5 DR. GRIMMETT: I favor reliance on the 6-month
6 data set, and it's my belief that the sponsor has provided
7 updates regarding the 9-month data set.

8 CHAIRMAN McCULLEY: Is there agreement with that?
9 Is there disagreement with that? And, again, I'm going to
10 tell you guys, if I don't hear anything, I'm going to assume
11 agreement. So don't sandbag me.

12 DR. BRADLEY: Can I get a clarification on the
13 question? It may sound facetious, but it's not. What do
14 you need to know from us at this point? Which data set
15 should we use to determine whether it was stable or not?

16 DR. ROSENTHAL: The issue is, when it first came
17 in, it looked as if there may be some degradation between
18 the 3 and the 6 months. They have now updated the data to
19 conclude significant 6-month data and reasonable 9-month
20 data, and that degradation does not hold. So at the time we
21 made up these questions, there was some concern whether it
22 was 3 or 6 months.

23 CHAIRMAN McCULLEY: It's a moot point now. It is.

24 DR. ROSENTHAL: Well, I mean, I--

25 DR. EYDELMAN: It's not really a moot point

1 because--

2 DR. ROSENTHAL: It's not really totally moot, but
3 I think we can make the decision ourselves. But we would
4 just--I mean--

5 CHAIRMAN McCULLEY: Well, our recommendation would
6 be 6 for the answer to the first one, and then to the second
7 point, additional 9-month data that you have, my sense is
8 that there's no need for additional 9-month data.

9 DR. EYDELMAN: I just want to clarify. The 9-
10 month update that was received was for the overall cohort.
11 We do not have any stratification by each indication. We
12 just have one key safety and efficacy outcomes for the
13 updated 9-month cohort.

14 CHAIRMAN McCULLEY: Well, relative to stability,
15 it seemed that they showed stability by 6 months. So I
16 would say anything you have beyond 6 months at 9 months is
17 gravy, unless you saw something that raised a flag.

18 DR. MAGUIRE: I think you should have it to 9
19 months until the stability issue I raised is understood,
20 make sure that the semantics are understood so we're not
21 having a semantic misunderstanding and a review of the data
22 both in the group that's in that table and in the other
23 group. So I think you should have all the people that were
24 promised us at 9 months included also, and then make a
25 decision because it's important for labeling.

1 CHAIRMAN McCULLEY: Is there agreement on that
2 point? Does that answer your question sufficiently for your
3 purposes?

4 DR. EYDELMAN: Yes. Thank you.

5 CHAIRMAN McCULLEY: Okay.

6 DR. EYDELMAN: Should approval be limited to +5
7 diopter spherical equivalent for the treatment of spherical
8 hyperopes? I just want to clarify. I'm not referring to
9 all three indications.

10 CHAIRMAN McCULLEY: Just spherical.

11 DR. EYDELMAN: Correct.

12 CHAIRMAN McCULLEY: Mike, I think you had strong
13 feelings. Would you like to give us your wisdom?

14 DR. GRIMMETT: Based on those factors, on my last
15 page of the summary notes, I answer yes, I would limit the
16 approval for 5 diopters for spherical hyperopes.

17 CHAIRMAN McCULLEY: Is there disagreement with
18 that? Joel?

19 DR. SUGAR: I'd like to disagree, partly because
20 of the numbers, the numbers of patients at the tails are
21 fewer and the expectations I think probably should be less,
22 and in looking at myopia in the past, we've always looked at
23 the tails with lesser expectations, and I think that it
24 makes most sense to approve this to the 6-diopter level,
25 although perhaps follow-up data on outcomes would be

1 worthwhile to get larger numbers. I would favor approving
2 for 6 diopters.

3 CHAIRMAN McCULLEY: Dr. Matoba?

4 DR. MATOBA: I agree with Dr. Sugar, but I'd like
5 follow-up data on the longer term for the 6 diopters plus
6 any retreatment data they have for those patients--more than
7 3 months, out to at least 6 months.

8 DR. BRADLEY: Jim?

9 CHAIRMAN McCULLEY: Yes, Arthur?

10 DR. BRADLEY: Just a point of clarification--a
11 question, actually, for Dr. Grimmatt. The recommendation,
12 is that based upon an efficacy failure or a safety issue?

13 DR. GRIMMETT: Given the low numbers that have
14 been mentioned multiple times, obviously it's difficult to
15 interpret the data conclusively. I was making the
16 recommendation not on one or the other but as a basis of the
17 multiple factors that I listed. So it was on the basis of
18 actually both. However, firm conclusions cannot be made
19 based on the low numbers in the higher subgroups.

20 CHAIRMAN McCULLEY: And the reality is, given the
21 patient population as it is as a whole, not just within this
22 PMA, it's going to be very difficult to get large numbers.
23 And one thing that Dr. Rosenthal mentioned before that is
24 another option would be to label--or approval to 5, but
25 allow with a flag coming up on the screen and so forth

1 access to the larger corrections. How would that as a
2 compromise fit? Dr. Pulido?

3 DR. PULIDO: I think that would be a very
4 reasonable compromise.

5 CHAIRMAN McCULLEY: So presumably the informed
6 consent would have to include that information for these
7 higher ranges, so it would ensure patient education more
8 than one would otherwise ensure.

9 Arthur?

10 DR. BRADLEY: The follow-up to Dr. Grimmitt's
11 response is that, as Dr. Salz mentioned earlier, I mean, I
12 think if the issue is one of reduced efficacy, I have no
13 problems with allowing them to treat higher hyperopes. If
14 the issue is one of safety, that is, the best corrected VAs
15 start to decline, then I think some limit should be placed
16 on the range.

17 CHAIRMAN McCULLEY: But we don't have enough
18 numbers to have confidence, really, for sure.

19 Marian?

20 DR. MACSAI: From what we have, there is this 10
21 percent rate of BSCVA loss of greater than or equal to two
22 lines for preop MRSE ranges greater than 5 diopters. But I
23 don't quite understand what Dr. Rosenthal is saying, and I
24 need clarification. Are you suggesting we recommend
25 approval for up to plus 5.00, yet leave the device open to

1 be used for anything over plus 5, just say it's off label?

2 DR. ROSENTHAL: No. No, it's not--

3 DR. MACSAI: That's what it sounded like.

4 DR. ROSENTHAL: No, it's not off label, because
5 it's only approved to plus 5. But what it is--

6 DR. MACSAI: But you're going to let the device
7 be--

8 DR. ROSENTHAL: You don't lock the device out at
9 5. You allow it to be used with a proviso that, one, there
10 may be significant risks associated with it--I mean,
11 significant--I mean, if they were really significant, we
12 should lock it out.

13 DR. MACSAI: Yes.

14 DR. ROSENTHAL: So that's a decision you have to
15 make. If you--

16 DR. MACSAI: Well, if we're not sure, then why
17 don't we just wait until we have more? I'm not sure I
18 understand what's being achieved by not making this
19 decision.

20 DR. ROSENTHAL: Well, I think what's being
21 achieved is that you disadvantage the patient between plus 5
22 and plus 6. If you lock it out, you say they cannot use it
23 at all.

24 CHAIRMAN McCULLEY: This is already--this would
25 not be the first time that this happened, Marian.

1 DR. ROSENTHAL: This happens in most lasers, Dr.
2 Macsai.

3 CHAIRMAN McCULLEY: A screen comes up that says
4 that it's beyond. Uh-oh, here comes the policeman.
5 Malvina?

6 DR. EYDELMAN: If I can just add now that--

7 DR. ROSENTHAL: Excuse me. Dr. Waxler just
8 pointed out it might never be studied at this high a range.
9 We would possibly prevent it from ever being used, and then
10 people would use it twice. You know, they'd do--to do a
11 plus 6 they'd do 2 and 4.

12 DR. MACSAI: Yes. Okay.

13 DR. ROSENTHAL: I mean, you know, we've had that
14 scenario, and we find that it's better to have a flag that
15 says proceed at your own risk.

16 DR. MACSAI: Well, it seems to me it's better to
17 have the flag, to say we've looked at it up to 6, and give
18 the data to the patients and the practitioners.

19 CHAIRMAN McCULLEY: Okay. That's reasonable.

20 DR. ROSENTHAL: That's a reasonable--

21 DR. MACSAI: And say we only know up to 6 and
22 don't do it over 6.

23 DR. ROSENTHAL: Well, no. It will not be--we
24 would not open it up to--we rarely open it when we have no--
25 in fact, we should never open it when we have no data

1 whatsoever. It's just when there is either very small
2 amounts of data or the data is problematic from generally an
3 effectiveness standpoint. If 50 percent of these eyes were
4 losing ten lines of visual acuity, we would block it.

5 DR. MACSAI: That's different.

6 DR. ROSENTHAL: Yes.

7 CHAIRMAN McCULLEY: And the numbers are so small,
8 the percentages are difficult. So is our recommendation to-
9 -Malvina?

10 DR. EYDELMAN: I'm sorry. I just started saying
11 something before. Since you have just recommended that 9
12 months additional data on spherical cohort alone be
13 submitted, that data can help us elucidate some of these
14 issues, because partially the problem was in the difference
15 of the outcomes at 3 months and 6 months. Once we get the 9
16 months outcomes for stratified, perhaps that can help us.

17 CHAIRMAN McCULLEY: All right. So what we would
18 say, then, would be approve to 5 with, you know, our opinion
19 that it should be opened to 6, anyway. And then if the data
20 supports, then approve to 6 once you have full data.

21 Is that a reasonable summary of our feeling?

22 DR. SUGAR: That's at least not what I'm
23 recommending. I'm recommending approval to 6 with
24 postmarket surveillance which may be obviated by the 9-month
25 data.

1 CHAIRMAN McCULLEY: Okay. But keep in mind, we
2 are strongly discouraged not to recommend postmarket
3 surveillance. It is a bear--

4 DR. ROSENTHAL: Well, no, this is postmarket
5 follow-up of existing patients, Dr. McCulley.

6 CHAIRMAN McCULLEY: If it's that--

7 DR. ROSENTHAL: That's not--I mean, you know, it
8 depends on how you want--

9 CHAIRMAN McCULLEY: Okay.

10 DR. ROSENTHAL: That's a postmarket--well,
11 whatever you want to call it.

12 VOICE: Approval follow-up.

13 DR. ROSENTHAL: Approval--but it's common and--

14 CHAIRMAN McCULLEY: It's not a postmarket study.

15 DR. ROSENTHAL: No. The problem--let me just--

16 CHAIRMAN McCULLEY: And you're not recommending a
17 postmarket study, Joel.

18 DR. SUGAR: If the 9-month data obviates that, no.

19 CHAIRMAN McCULLEY: Okay. All right. So I think--
20 -does that adequately answer your question, Malvina?

21 DR. EYDELMAN: Yes. Thank you.

22 CHAIRMAN McCULLEY: Okay. Next question.

23 DR. EYDELMAN: Again, what is the appropriate
24 stability time point, this time for hyperopic astigmatism
25 cohort? And in this same light, is additional 9 months data

1 needed? Once again, the update was for the overall only and
2 not stratified.

3 CHAIRMAN McCULLEY: Is the opinion any different
4 here than it was for sphere?

5 [No response.]

6 CHAIRMAN McCULLEY: So same opinion.

7 DR. EYDELMAN: Is approval recommended for the
8 full refractive range of the hyperopic astigmatism?
9 Currently it's up to plus 6 sphere and up to minus 6
10 cylinder.

11 CHAIRMAN McCULLEY: Mike, taking into
12 consideration our previous discussion, what would be your
13 studied opinion here?

14 DR. GRIMMETT: There are these same issues we had
15 on the table with the spherical hyperopia group with the low
16 numbers, unable to make firm conclusions. At a minimum, I
17 would favor what Dr. Sugar has put on the table regarding
18 some type of postmarket surveillance.

19 I did have concerns regarding the best corrected
20 visual acuity loss in the higher ranges. The sponsor did
21 answer some of those, at least--I can't recall off the top
22 of my head, but at least half of those they said came within
23 one line of best spectacle corrected visual acuity at other
24 visits prior to retreatments, for example. And given that
25 additional information that I saw today, I would be

1 satisfied with the recommendation Dr. Sugar has previously
2 made.

3 CHAIRMAN McCULLEY: Can you translate that into
4 this group and that be an adequate response to your
5 question, Malvina?

6 DR. EYDELMAN: Yes.

7 CHAIRMAN McCULLEY: Okay. Next question.

8 DR. EYDELMAN: Is the sample size of the mixed
9 astigmatism cohort adequate for the purposes of determining
10 safety and effectiveness?

11 CHAIRMAN McCULLEY: Mike? Joel? Somebody over
12 there? Jose? Anyone? Anyone have a comment?

13 DR. MACSAI: I think the numbers are too small for
14 the mixed astigmatism cohort. I'll throw it out. Now we
15 can argue about it?

16 CHAIRMAN McCULLEY: How often do you see mixed
17 astigmatism in the patient population, virgin mixed
18 astigmatism? Not a whole heck of a lot of them out there.
19 We're creating more now with our procedure--well, I'm not
20 being a smart aleck. That's reality. We're creating more
21 sequential mixed astigmatism than there are virgin.

22 DR. MACSAI: I don't think they're such a rare--

23 CHAIRMAN McCULLEY: it's not a big patient
24 population.

25 DR. MACSAI: I think they're--well, I don't have

1 statistics to answer it, so I'm going to refrain. I have no
2 scientific basis.

3 CHAIRMAN McCULLEY: Well, it's not a common
4 problem, and given this not in isolation but with the other
5 information we have, I think their numbers are pretty good
6 numbers for outcomes on primary, virgin, mixed astigmatism.

7 Joel?

8 DR. SUGAR: Given that this request was for a
9 continuum and that we've made this a subpopulation, not the
10 sponsor, and given that this is a fraction of the spectrum
11 but not in their--in their treatment algorithm, really not a
12 different disease as much as if they were treating sphere
13 first and then cylinder second and getting a thinner bed, I
14 think that this should be considered as part of the
15 spectrum, and like the 5- to 6-diopter segment, this is a
16 segment of the population that it would be nice to get--not
17 nice, but we should look at the 9-month data on a larger
18 population than we have. But we should approve it for the
19 full range that was requested.

20 CHAIRMAN McCULLEY: Then if the 9-month data
21 doesn't raise--

22 DR. ROSENTHAL: Excuse me, Dr. Sugar. You're not
23 going to get more than 68 eyes. I mean, you know, there's
24 no way we--

25 DR. SUGAR: That's what I'm saying, but in the

1 data presented to us, there were six eyes at 9 months.

2 DR. ROSENTHAL: But do you have enough data with
3 68 eyes? If you believe--

4 DR. SUGAR: We had 46 eyes, I--I'm sorry, 64 eyes.

5 DR. ROSENTHAL: Yes, okay.

6 DR. SUGAR: I think that in this segment of the
7 population, looking at it as a continuum, as we have, that
8 we have sufficient data for this segment of the hyperopic
9 astigmatic population, yes.

10 CHAIRMAN McCULLEY: But you want 9-month data, and
11 if the 9-month data doesn't introduce any new issues, then
12 we're fine with this number.

13 DR. SUGAR: Exactly.

14 DR. ROSENTHAL: I want to clarify this panel's
15 sense that you believe this is a continuum, that this
16 treatment of mixed astigmatism does not have to be
17 considered a separate, quote, indication.

18 DR. SUGAR: That's what I feel, yes. We haven't
19 gotten a consensus from the panel.

20 CHAIRMAN McCULLEY: But that becomes a labeling
21 issue, though, doesn't it?

22 DR. ROSENTHAL: No, it becomes a--

23 [Simultaneous conversation.]

24 CHAIRMAN McCULLEY: If we think the safety and
25 efficacy on this group, given its position, is enough--

1 DR. ROSENTHAL: It becomes an issue on how we deal
2 a level playing field with other companies. And it depends
3 on the interpretation of the profiles. If you believe this
4 is all a continuum, then it's quite legitimate, as the
5 company originally proposed, to include this group in what
6 they call hyperopic astigmatism. But if you believe that--
7 because of the profile issues related to this, the other
8 companies are going to have the profile issues as well, and
9 we're going to have to deal with them separately.

10 DR. SUGAR: I'm saying in the context of this
11 treatment algorithm, yes. If they have a different
12 treatment algorithm where you treat sphere and then cylinder
13 or however you choose to treat mixed astigmatism--

14 DR. ROSENTHAL: That's fine.

15 DR. SUGAR: --that's a different issue.

16 CHAIRMAN McCULLEY: Yes?

17 MS. HOANG: We realize that the sponsor has made
18 an argument that it is a continuum of treatment, and we
19 would like to make the following comment.

20 DR. DRUM: Bruce Drum. I'd like to try to clarify
21 what we consider to be the critical differences between the
22 different indications. Regardless of how the ablation is
23 accomplished, there are certain qualitative differences that
24 separate the different indications. Mixed astigmatism in
25 particular was defined earlier by everybody involved as a

1 positive refractive error in one axis and a negative
2 refractive error in the orthogonal axis.

3 There are qualitative differences between that
4 shape and between all other shapes of refractive correction.
5 For example, if you look at hyperopic astigmatism with
6 positive corrections in both axes of different magnitudes,
7 there's a positive curvature in both places. As you go past
8 the critical point where you go into mixed astigmatism and
9 one axis becomes negative, then you reach an ambiguity. If
10 you're trying to define mixed astigmatism as a subpopulation
11 of hyperopic astigmatism, it becomes ambiguous because you
12 could equivalently define it as myopic astigmatism if you
13 pick the other convention.

14 CHAIRMAN McCULLEY: My point about the 64 being an
15 adequate number is that it's not being considered in
16 isolation. We have other data with the laser for myopic
17 astigmatism and hyperopic astigmatism. That's one point
18 that makes me--if this were the only thing being requested
19 for a laser and we had no other data, I would be
20 uncomfortable with 64 patients.

21 DR. DRUM: Yes, I agree.

22 CHAIRMAN McCULLEY: Sixty-four patients in the
23 spectrum of the others on either side, whether it's truly a
24 continuum or not, is not relevant really to this question.
25 It may be for you guys and your regulatory problems, and I

1 don't think that's for us to solve today. But I think the
2 answer to this question is yes, that 64 patients at 9 months
3 is sufficient, partly because it's sandwiched between the
4 other two groups, however you want to term it, whether it's
5 a continuum or there's a discontinuity on either side.

6 DR. DRUM: Right. Well, the issue of whether
7 there are different safety or effectiveness issues related
8 to these different indications is another question.

9 CHAIRMAN McCULLEY: Right. And I don't object to
10 this being a separate, you know, consideration and separate
11 label. I just think that 64, given the fact that we have
12 other data that could supplement this, and the reality that
13 there are not a lot of virgin mixed astigmats out there, the
14 64 is adequate. If we get the 9-month data and it doesn't
15 bring up any additional questions or concerns, it would be
16 adequate.

17 Arthur, and then Leo.

18 DR. BRADLEY: Yes, I think the sponsor has given
19 us a theoretical argument as to why there's nothing
20 fundamentally different between mixed and hyperopic
21 astigmatism, and the impression that I get from the data set
22 is that we're not seeing any striking difference between the
23 results in these two groups. And I think, therefore, we're
24 going to have to make a special effort to continue this
25 distinction, it seems to me, because it's not clear that

1 it's there.

2 DR. ROSENTHAL: May I just clarify what Dr.
3 Bradley said? It's the treatment of hyperopic and mixed
4 astigmatism, not the fact that hyperopic and mixed
5 astigmatism are not suffered. Of course--

6 DR. BRADLEY: I stand corrected. That's what I
7 meant.

8 DR. ROSENTHAL: Okay. Thank you. I wanted to be
9 sure, because that's very important in our evaluation of the
10 issue.

11 CHAIRMAN McCULLEY: Leo?

12 DR. MAGUIRE: One argument does exist for
13 thinking, at least giving some thought to having a bigger
14 group looked at. That comes in context of the fact that it
15 is a continuum, and at other places on the continuum there's
16 a difference between anticipated and achieved results in
17 terms of induced astigmatism. Again, I emphasize the simple
18 hyperopes have a high level of induced astigmatism 1 diopter
19 and greater. Okay? It's a minority, but it's a significant
20 minority. And so the question comes up: Does this same
21 type of thing occur in other parts of the continuum? And if
22 it does, do you have adequate sample size to detect a 7
23 percent incidence of induced astigmatism of 1 diopter or
24 greater? And that would be something that I think the
25 statistical people at FDA should look at before they make a

1 decision.

2 CHAIRMAN McCULLEY: Okay. So you have our
3 response with the qualification. Does that adequately
4 answer your question?

5 DR. ROSENTHAL: Mm-hmm.

6 DR. EYDELMAN: Does stability of the manifest
7 refraction cylinder adequately establish overall stability
8 for this cohort? If not, what additional stability analyses
9 are needed?

10 CHAIRMAN McCULLEY: Who wants to field that one?

11 DR. MAGUIRE: If I can, I would make the same
12 comments I did about stability on the earlier component.

13 CHAIRMAN McCULLEY: Anyone else? Joel? Or, no,
14 that's not your hand. That's the mike sticking up.

15 Anyone else have any--Arthur?

16 DR. BRADLEY: Perhaps I should just raise a
17 dissenting view at this point. I'm struggling to be
18 convinced that we need 9-month data to establish stability
19 in any of these data sets. It seems to me that looking at
20 most of the primary outcome measures, we have stability at 3
21 months.

22 CHAIRMAN McCULLEY: Well, going backwards you do.
23 But you have to have 6-month data to know it's stable at 3.

24 DR. EYDELMAN: It seems like the panel might not
25 have understood my question, if I may just clarify it. The

1 question here refers to the method of evaluation of
2 stability for the mixed astigmatism, whether it is best
3 achieved by manifest refraction cylinder. We're not talking
4 about at what time point but how best to evaluate it.

5 DR. BRADLEY: I would say yes.

6 DR. GRIMMETT: This is Dr. Grimmett. I agree. I
7 think the answer's yes.

8 CHAIRMAN McCULLEY: Okay. Next question.

9 DR. EYDELMAN: What is the most appropriate
10 stratification of key safety and efficacy outcomes for mixed
11 astigmatism cohort?

12 CHAIRMAN McCULLEY: So rather than stratifying by
13 manifest spherical equivalent--

14 DR. EYDELMAN: Correct.

15 CHAIRMAN McCULLEY: --what would our
16 recommendation for stratification be for this group?

17 DR. EYDELMAN: Correct.

18 CHAIRMAN McCULLEY: Okay. Suggestions? Mike?

19 DR. GRIMMETT: I believe this is where the FDA
20 asks for the stratified outcomes in 1-diopter increments of
21 the difference between the absolute magnitudes. Is that
22 what you had asked for here?

23 DR. EYDELMAN: Correct.

24 DR. GRIMMETT: I don't have any other additional
25 suggestions, but I would be interested what Arthur Bradley

1 has to say on this.

2 CHAIRMAN McCULLEY: That's called turfing it to
3 you.

4 DR. BRADLEY: I must be having a slow afternoon.
5 I'm struggling with the question again. Sorry about this.
6 But you want to know--

7 CHAIRMAN McCULLEY: The others were stratified by
8 1 to 2, 2 to 3, so forth, with .99's thrown in there. But
9 manifest refractive spherical equivalent is how the groups
10 have been stratified. And the desire is to stratify within
11 mixed astigmatism, how best to stratify within mixed
12 astigmatism because the spherical equivalent doesn't work.

13 DR. BRADLEY: I would say without doing, as I've
14 suggested, a formal three-dimensional analysis, you really
15 go with the amplitude of the astigmatism.

16 DR. ROSENTHAL: The full amplitude.

17 DR. BRADLEY: Yes. Yes. By the way, this issue
18 of absolute amount of--

19 DR. ROSENTHAL: The full amplitude of--

20 DR. BRADLEY: The full amplitude, yes.

21 DR. ROSENTHAL: That's fine.

22 DR. BRADLEY: I wouldn't go with this absolute
23 magnitude.

24 DR. ROSENTHAL: That's fine. Okay. We want to be
25 sure.

1 CHAIRMAN McCULLEY: And you went with absolute.
2 DR. ROSENTHAL: No--yeah, we went with absolute.
3 DR. EYDELMAN: With a difference--
4 DR. ROSENTHAL: We went with absolute.
5 CHAIRMAN McCULLEY: I didn't understand what you
6 did.
7 DR. ROSENTHAL: We went with absolute, but--
8 CHAIRMAN McCULLEY: We're saying full.
9 DR. ROSENTHAL: Okay. Thank you. That's what we
10 actually thought after we thought we had--
11 CHAIRMAN McCULLEY: Never mind.
12 DR. ROSENTHAL: We thought there was another
13 option. Okay.
14 CHAIRMAN McCULLEY: Okay. You got it. The full
15 amount of the astigmatism. The difference in power between
16 the two meridians.
17 DR. MACSAI: And the full attempted versus the
18 full achieved.
19 CHAIRMAN McCULLEY: Yes, full attempted versus
20 full achieved.
21 Any other comments to that?
22 DR. EYDELMAN: Along the same line, then, what
23 additional analysis, if any, do you recommend for evaluation
24 of this cohort?
25 CHAIRMAN McCULLEY: Are there any others? Arthur,

1 do you think it's reasonable to request your three-
2 dimensional?

3 DR. BRADLEY: I think at a minimum you should be
4 able to do an analysis of your vector data without having to
5 compress it to one dimension. I mean, you have your two-
6 dimensional vector analysis already done, and I think it's
7 reasonable to look at that.

8 DR. EYDELMAN: That has been done.

9 DR. BRADLEY: That's correct. So you are asking
10 what additional, and I think most of the discussion has
11 centered around a one-dimensional, either the magnitude--and
12 I think you do need to consider the magnitude and the axis
13 that will tell you, for example, whether there's a
14 systematic error in the correct procedure.

15 DR. EYDELMAN: My written review addressed the
16 vector analysis of the mixed astigmatism.

17 CHAIRMAN McCULLEY: It did, but here you are
18 asking what we thought you ought to do, and we're just
19 saying we ought to do what you have already done there.
20 Just so you don't think we don't think you ought to do it.

21 DR. EYDELMAN: Next question. Is the presentation
22 of patient symptoms at 3 months or later sufficient, or
23 should the sponsor be requested to resubmit the patient
24 questionnaire outcomes stratified by the various time points
25 for each of the cohorts?

mc

1 DR. SUGAR: Didn't they do that?

2 DR. EYDELMAN: They resubmitted the patient
3 questionnaire for the overall cohort--

4 CHAIRMAN McCULLEY: But not stratified by time?

5 DR. SUGAR: No, not stratified--

6 DR. EYDELMAN: They stratified it--

7 DR. SUGAR: Treatment.

8 DR. EYDELMAN: Correct.

9 DR. ROSENTHAL: They stratified it by time, but
10 they didn't stratify it by indication--I mean, by--

11 VOICE: They should.

12 DR. ROSENTHAL: They should, and you feel they
13 should.

14 DR. EYDELMAN: Are there any additional labeling
15 recommendations?

16 DR. GRIMMETT: Of course, I would endorse the ones
17 that I stated in my summary comments.

18 VOICE: As would I.

19 CHAIRMAN McCULLEY: We have a whole bunch. Is
20 this the last of your questions?

21 DR. EYDELMAN: Yes, it is.

22 CHAIRMAN McCULLEY: Okay. Can we turn the lights
23 back on? And this is probably where we need to start to put
24 things up on the top end.

25 Well, what she's asking for now, are there any