

1 dispersion syndrome; that is, myopia young age in  
2 Caucasian race. Pigment dispersion syndrome is at  
3 least as common in women as in men.

4 One study quoted about a 2-1/2 percent  
5 incidence of pigment dispersion in Caucasians. Simply  
6 using this figure based on the number of Caucasians in  
7 the STAAR PMA, we'd expect six in this study to have  
8 pigment dispersion. The Sponsor reports zero, both  
9 before and after ICL implantation. Let's look to the  
10 literature.

11 A published study found pigment dispersion  
12 in the angle in 9 of 58 eyes, or 15-1/2 percent at 18  
13 months. The authors postulated that the STAAR ICL  
14 pushes the iris anteriorly, and optic iris chafing  
15 leads to pigment dispersion syndrome in a subset of  
16 patients.

17 A 1998 study, using ultrasound after ICL  
18 implantation, found angle narrowing in all eyes, and  
19 peripheral anterior synechiae in 2 out of 9 eyes, or  
20 22 percent. The ICL was in wide contact with the iris  
21 in all eyes.

22 For this study, I reviewed the submitted

1 PMA materials, and reviewed both the pre-op and  
2 post-op clinical study report forms. I didn't find  
3 any gonioscopy data, which I was shocked to see that.  
4 I also didn't find any ultrasound data presented to  
5 determine angle anatomy alterations following the ICL.  
6 It's my opinion that the lack of these data is a  
7 disservice to present and future patients with the  
8 STAAR ICL, and represents a major study design error.

9 Gonioscopy can assess angle pigment  
10 deposition, a sensitive and common finding in pigment  
11 dispersion syndrome. Perhaps no patient was diagnosed  
12 with pigment dispersion syndrome because no one looked  
13 at the angle post-op.

14 Moreover, gonioscopy can determine angle  
15 narrowing and synechiae. Further, if no gonioscopy  
16 examinations were performed, other relevant features  
17 could be missed, vascularization and other  
18 preoperative abnormalities.

19 The theoretical risk to the angle can be  
20 easily surmised given the design and intended use of  
21 this phakic IOL, and it's my belief that the initial  
22 study design should have included gonioscopy, whether

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1 or not it was mandated by the FDA.

2 Let's review issues related to pupil  
3 diameter and the lens optic diameter. It's well known  
4 that dim illumination mydriasis can be robust in the  
5 young. Dr. Vukich indicated that when this study was  
6 designed, that those parameters were not well known.  
7 Being an old guy, I beg to differ. Back in about  
8 1993-94, I reviewed issues related to pupil diameter  
9 with small optical zone radial keratotomy. My  
10 literature review at that time revealed that the  
11 mydriasis being robust in the young was documented,  
12 well know, and in the literature at that time. I  
13 believe that predates the design of this particular  
14 study.

15 STAAR's study cohort ranged from 22 to 45  
16 years of age, and we've heard that the lens optic  
17 diameter is 465 to 55. Given the young age of the  
18 cohort, as Dr. Bradley already noted, it's reasonable  
19 to expect that some patients will have dim  
20 illumination pupil diameters that exceed the lens  
21 optic diameter. We, therefore, have an expectation  
22 that some patients may experience halos and dim

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1 illumination, or have nighttime visual aberrations.

2 Looking to the literature, Arne found a  
3 higher frequency of halos with small optic diameter  
4 ICLs. The rate of halos correlated to the difference  
5 between the scotopic pupil diameter and the optical  
6 zone size. Due to these halos, these authors  
7 recommended intentional under-correction for high  
8 myopia; that is, using a larger optic diameter lens  
9 followed by LASIK.

10 Hence, another study design error in this  
11 PMA is the absence of pupil size measurements.  
12 Relevant analysis should have included the rate of  
13 visual aberrations with increasing optic pupil  
14 mismatch. Regrettably, this was not performed for our  
15 review.

16 In the absence of this pupil size  
17 information, the best we can do is stratify the  
18 patient's symptoms by the lens optic diameter. I  
19 couldn't find this information in the materials given  
20 to me, but it should be required for later FDA review.  
21 Also, each symptom category should be reported  
22 separately; that is, separately none and mild, rather

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1 than lumping the categories in the current tables. Of  
2 course, this information presumes that the small lens  
3 optic patients do not have skewed pupil sizes one way  
4 or the other. We'll simply never know.

5 Let's go on to endothelial cell loss. The  
6 threshold analyses that I presented in Appendix 1 of  
7 my written review show maximum rates of annual cell  
8 loss to reach various target levels at the time of  
9 death. Clearly, there's many assumptions that are  
10 made, including an annual instantaneous cell loss, and  
11 that it's linear, and it doesn't include information  
12 regarding stem cell repopulation. However, using  
13 these figures, if we desire a 1500 cell for millimeter  
14 square density at death, a .9 percent annual loss rate  
15 is the maximum, inclusive of all age ranges; that is,  
16 the 20 to 30 year old range. And if we desire an 800  
17 cell per millimeter square density at death, a 1.9  
18 percent annual loss is the maximum.

19 It's important to remind ourselves that 50  
20 percent of patients will have endothelial cell  
21 densities that fall below the normal mean cut-off  
22 values; and, therefore, younger patients, that 20 to

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1 30 age group, have a significantly higher risk of  
2 running out of endothelial cells during their lifetime  
3 if these rates are continuous. And now to the PMA  
4 itself.

5           Regarding the study population, the total  
6 eyes show with the blue bars indicate very good  
7 follow-up. I certainly recognize the difficulty of  
8 carrying out such a large study for an extended period  
9 of time, and commend the Sponsor for their efforts.  
10 The purple bars show endothelial data on approximately  
11 200 eyes, with a large drop-off at the 48 month  
12 interval shown out here as 67 eyes.

13           I find it ironic, some studies we reveal  
14 at panel only have 6 and 12 month data, and we're  
15 always wrestling with not enough data. And here a  
16 Sponsor has run a 3 and 4 year study, and we're still  
17 wrestling with not enough data. I just found that  
18 amazing.

19           Unfortunately, the endothelial data in the  
20 written PMA have varying ends, and there's no  
21 consistent cohort of eyes followed through each and  
22 every examination interval. The data we've seen today

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1 with that 37 eye consistent cohort was not provided to  
2 me in the materials that I reviewed. That made the  
3 evaluation difficult.

4 Just one housekeeping item, and I believe  
5 Malvina already alluded to this. The inclusion  
6 criteria had a stable refraction within a half diopter  
7 over the prior year. The indications for use  
8 statement had a 1 diopter over the prior year,  
9 obviously, needs to be matched or reconciled.

10 Regarding the exclusion criteria, we know  
11 that phakic IOLs can alter the corneal endothelial.  
12 Dr. Macsai alluded to this. The corneal endothelial  
13 status was omitted from the exclusion criteria, and  
14 given the young age of these patients, I believe it  
15 would be a relevant material fact to be considered  
16 prior to implantation of this device.

17 Certainly, if a young patient had an  
18 abnormal endothelial layer, I would not recommend this  
19 device as a clinician. There is no question that I  
20 wanted pre-op specular endothelial analysis for this  
21 cosmetic elective procedure, where the alternative is  
22 glasses or contact lenses.

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1           On to some safety issues. Let's discuss  
2 the learning curve associated with phakic IOL  
3 implantation. I believe we're all in agreement that  
4 the labeling should include relevant learning curve  
5 issues. Of the 13 upside down lens insertions, 11  
6 occurred within the investigator's first 22  
7 procedures, 6 out of 13 developed in AST in the early  
8 post-op period. Of the 14 eyes that developed  
9 anterior subcapsular cataracts, most occurred within  
10 each investigator's first 8 surgical cases. One  
11 investigator accounted for a disproportionate share of  
12 the ASCs, a 9.4 percent rate, and that same  
13 investigator accounted for both cataract extractions  
14 in the study. To lessen the impact of learning curve  
15 issues for the patient, I'd favor specialized course  
16 training or case supervision by an experienced surgeon  
17 for early cases.

18           On to change in best spectacle corrected  
19 visual acuity. As compared to the lower dioptic  
20 groups, there are larger post-op gains of best  
21 corrected visual acuity, 20/20 or better, in the high  
22 myopia group. For the less than 7 diopter group shown

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1 in the orange, there is an 8.3 percent gain pre-op  
2 among 36. For the 7 to 10 diopter group shown in the  
3 maroon, there's a 15.6 gain pre-op among 36, and for  
4 the greater than 10 diopter group shown down here in  
5 the blue, there's about a 20.4 percent gain pre-op  
6 among 36. These are findings strongly argued for an  
7 induced magnification effect as a result of the  
8 surgery.

9 In looking at greater than or equal to one  
10 line of best corrected visual acuity loss, high myopes  
11 have an increased rate of vision loss with time as  
12 compared to lower myopes. And we've already heard  
13 that for this particular group, a one line loss is the  
14 equivalent of a two line loss due to induced  
15 magnification as a result of the surgery.

16 The rate of greater than one line loss  
17 goes up to about 16 percent. I'm not sure why that  
18 would exactly be. I don't know if that has to do with  
19 lens optic pupil mismatch or other issues, but I'm not  
20 sure it's well delineated. It's certainly not clear  
21 in my mind as the ultimate etiology of that.

22 Another way to look at the same issue, the

1 mean improvement in lines of vision, high myopes with  
2 time decline in improvement starting at 6 months, one  
3 line improvement down to .4, two line improvement at  
4 36 months. Certainly, appropriate labeling should  
5 mention this trend.

6 On to interocular pressure, 20 of 526  
7 eyes, or 3.8 percent had pressure spikes in the early  
8 post-op period, 11 reached 40 to 50, 4 reached 55 to  
9 58, and 1 reached a whopping 65 millimeters of  
10 mercury. Most of the spikes occurred by day one or  
11 two, 17 needed additional YAG, 3 required AC washout  
12 for retained viscoelastic. Clearly, these pressure  
13 elevations are not trivial. Myopic disks are perhaps  
14 slightly more susceptible to damage from elevation of  
15 IOP than ametropic or hyperopic disks.

16 Patient and physician labeling should  
17 highlight the issue in order to appropriately plan  
18 early post-op exams. As a clinician, I might consider  
19 the use of Diamox on a case-by-case basis.

20 With regard to chronic pressure elevation,  
21 the overall cohort shows an increasing trend for  
22 patients to experience an increase in pressure greater

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1 than 5, looking at the graph, at 6 months about a  
2 little under 3 percent, and at 36 months something  
3 over 6 percent, 6-1/2 percent had a change in baseline  
4 pressure.

5 Pre-op, looking at patients with a  
6 pressure greater than 21, about 3 percent had  
7 pressures greater than 21, and at 36 months about 6  
8 percent had pressures greater than 21. Two patients  
9 were diagnosed with glaucoma and treated topically.

10 Given the potential for the STAAR lens to  
11 alter pressure regulation for the factors previously  
12 mentioned, I'm concerned about this finding. We must  
13 recognize these recipients are young, expected to live  
14 many future years. At a minimum, labeling should  
15 emphasize this particular issue. I again note that  
16 the STAAR study omitted gonioscopy for a device that  
17 affects the angle. Gonioscopy can assess pigment  
18 deposition, a sensitive and common progressive finding  
19 in pigment dispersion syndrome. Angle grade and  
20 synechiae formation are also relevant findings.  
21 Inexplicably, gonioscopy wasn't done. If I were a  
22 clinician, I would be doing gonioscopy.

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1           The corneal endothelial data - in the  
2 materials provide there was no true consistent cohort  
3 data for each and every examination interval. There  
4 was fluctuating denominators at the various  
5 examination intervals, and this made our analysis  
6 difficult. We've seen data today on 37 eyes that had  
7 consistent cohort data, but the remainder of the  
8 application does not.

9           While this is not a consistent cohort of  
10 eyes, there appears to be progressive endothelial cell  
11 loss over time. The total at four years is  
12 insufficient to make conclusive statements, but the  
13 cell loss does not stabilize over the study period.  
14 These cell loss rates, if continuous, constitute a  
15 serious safety issue that may jeopardize approval of  
16 this device.

17           Looking at the 154 eye consistent cohort  
18 at year 3, pre-op to 36 months, 8.9 percent loss, that  
19 was higher than the table we just looked at with 8.4  
20 percent. It took me a long time to figure out that  
21 there were two disparate groups that had an "N" of 57,  
22 and both reported 4 year loss rates, and both were

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1 called the consistent cohort. Two groups, pre-op to  
2 48 months, there was a 9- 1/2 percent endothelial  
3 loss. Three year to four year there was a .041  
4 percent endothelial gain, with the upper limit of the  
5 90 percent confidence interval at 1.43 percent loss  
6 per year.

7 It's this one isolated group, as we've  
8 heard, which the Sponsor is making the argument for  
9 stability in conjunction with the morphometric data  
10 that Dr. Edelhauser reviewed.

11 Let's look closer at this 57 eye cohort.  
12 This is a histogram that was in the material  
13 somewhere, that outlines where these eyes fell in  
14 terms of cells gained or cells lost. The mean cell  
15 density increased by one cell. Overall, just looking  
16 on the number of eyes on either side as zero, 31 eyes  
17 lost cell density, and 26 eyes gained. More eyes lost  
18 zero to five here at 21, than gained zero to five.  
19 It's about even on either side of 5 to 10, 8 versus 7.  
20 This is the group that had me wondering.

21 Here's a group out here gaining 10 to 15  
22 percent of cells, versus only one eye losing 10 to 15

1 percent. Of these 7 histogram analyses in the  
2 application, this is the only one that had more eyes  
3 gaining 10 to 15, than losing 10 to 15. Certainly,  
4 I'm willing to accept random measurement error that  
5 leads to an evenly matched set of gains and losses.  
6 That is a true bell curve due to precision errors  
7 measuring endothelial cell loss, but I can't come up  
8 with a physiologic reason that five eyes have truly  
9 gained a sizeable percentage of endothelial cells in  
10 12 months. I'm wondering whether these big ticket  
11 outliers up here at 10 to 15 percent skewed the mean  
12 data and falsely elevated it, leading us to a  
13 conclusion of stability.

14 We've heard from Dr. Gray, and his  
15 comments were greatly appreciated by me. I place great  
16 emphasis on statistical analysis of the data. He  
17 noted that simple comparison of the two to three year  
18 loss versus the three to four year loss is not  
19 appropriate due to the likelihood of producing  
20 negatively correlated observations. And he mentioned  
21 that multiple ways by saying that the three year loss  
22 was lower than the other data points.

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1           He also noted there was not strong  
2           statistical evidence that the cell loss levels off  
3           after year three. Additionally, of the 57 eye cohort  
4           with both three and four year data, 10 out of 57, or  
5           17-1/2 percent had more than 5 percent cell loss over  
6           12 months. Those are pretty big numbers if those are  
7           true for a young cohort.

8           Based upon these data, I remain  
9           scientifically unconvinced that this procedure  
10          provides a reasonable assurance of safety for the  
11          corneal endothelium in the long run. The  
12          preponderance of evidence that we were offered was  
13          weighted toward an unsafe level of endothelial cell  
14          loss, that if continuous, would jeopardize the safety  
15          of a future interocular procedure or cause corneal  
16          edema during the patient's lifetime, or both. I think  
17          we're all in agreement, we need a larger four year  
18          sample size. I would agree that ongoing endothelial  
19          surveillance to year five would be desirable, given  
20          the youth of the cohort.

21                 I'll talk briefly about anterior chamber  
22          cell depth. We see that the endothelial loss in eyes

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1 with shallow anterior chambers was 12.2 percent over  
2 three years, while the loss was 8.4 percent for eyes  
3 with anterior chambers greater than three. As Dr.  
4 Macsai noted, a 50 percent increase in shallow  
5 chambers. I would not necessarily disagree with an  
6 abundance of caution approach to limit the device to  
7 eyes with anterior chambers greater than 3.

8 It's worthwhile noting that only 5-1/2  
9 percent of the total study cohort would be excluded by  
10 this limitation. And, therefore, I don't believe it's  
11 an onerous limitation that would exclude large numbers  
12 of patients. I think it's reasonable to do that.

13 Something interesting in this 57 eye  
14 cohort, in addition to looking at the histogram, if we  
15 look at the anterior chamber depths for 50 of these  
16 eyes in that cohort with three to four year data, 50  
17 eyes had an anterior chamber depth greater than 3  
18 millimeters. They gained .3 - excuse me - they lost  
19 .3 percent in endothelial cell loss from year three to  
20 four, and there were 7 eyes with an anterior chamber  
21 depth that was shallow, and they had a 2.9 percent  
22 gain in endothelial cells between years three to four.

1           From my vantage point, that didn't make  
2 sense. That was a counter-intuitive result that  
3 contradicts the generalized study results of a higher  
4 rate of loss in the shallow AC group. From my vantage  
5 point, something smells wrong with that 57 eye cohort.  
6 I would love for that four year cohort to be larger so  
7 that it would even it all, so that we'd have a better  
8 statistical sense of what's going on.

9           On to effectiveness, and at this point I'm  
10 going to stipulate to Dr. Slade's excellent  
11 presentation on effectiveness, and we're not going to  
12 go over all this data, so yadda-yadda-yadda, the  
13 procedure seems effective. That's enough of that.

14           In terms of willingness to have the ICL  
15 again, 5.6 percent less than 7 diopters were not  
16 willing to undergo it again. And in the greater than  
17 15 diopter group, all patients were willing to undergo  
18 it again, despite poor effectiveness and high rate of  
19 complications. I interpret this finding just to mean  
20 that low myopes are less desperate for the surgery, as  
21 compared to high myopes who appreciate help of any  
22 kind, even though it may not be perfect.

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1                   And in conclusion, this does appear to be  
2                   an effective device to reduce myopia. We must be  
3                   reasonably sure that the endothelial cell loss does  
4                   indeed stabilize following ICL implantation. It's  
5                   critical to recognize that these devices are intended  
6                   for a young population with 50 plus years to go. We  
7                   can't afford an epidemic of bullous keratopathy for a  
8                   cosmetic elective procedure.

9                   I'm also concerned that while the  
10                  morphometric data show that we don't have a change in  
11                  pleomorphism or polymegathism, what I'm concerned  
12                  about is that there's evidence to suggest that younger  
13                  corneas may blunt our ability to see those changes.  
14                  I'm just wondering whether we're not seeing much of a  
15                  change for chronic stress simply due to the fact that  
16                  the cohort is a bunch of young corneas.

17                  Dr. Edelhauser, I believe, was in general  
18                  agreement that younger corneas are robust, and may not  
19                  show stress factors as readily as an older cornea, so  
20                  I'm concerned that the data does not have statistical  
21                  evidence to show that it tapers off for sure, and I'm  
22                  concerned that the younger corneas may blunt our

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1 ordinary morphometric data that would ordinarily tell  
2 us there's stress.

3 I certainly need convincing with a larger  
4 "N" for the four year endothelial data one way or  
5 another. I think that number needs to be bigger.  
6 Thank you very much for your attention, and I  
7 apologize if it was redundant.

8 DR. WEISS: Thank you, Dr. Grimmett, for  
9 your usual detailed, insightful reviews.

10 We're going to now go on with panel  
11 discussion of this PMA. I'm going to ask the FDA if  
12 they'd be so kind to come to the podium. And I would  
13 also request that we go out of order of your  
14 questions. There's a method to my madness, so I'd  
15 like to start with question 3, which is a discussion  
16 of how to decide what size to put in the eye. And in  
17 terms of whether the currently recommended method  
18 measuring the white-to-white, which was recommended by  
19 the sponsor is an appropriate way to do it. And if  
20 not, what does the panel recommend.

21 I will remind you just in terms of what  
22 we've heard from our reviewers, Dr. Macsai was

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1 recommending using the Orbscan or something similar,  
2 because the white-to-white is not very accurate. And  
3 Dr. Grimmett also agreed, the white-to-white was not  
4 very accurate. But I'd like us as a panel to  
5 determine whether we're going to recommend that the  
6 labeling include the way the panel -- the way the  
7 sponsor did the study, which is measuring white-to-  
8 white, or do we want something else. Dr. Sugar.

9 DR. SUGAR: I'd like to recommend that we  
10 recommend no changes from the Sponsor has recommended,  
11 given that we don't have anything better that I'm  
12 aware of. Certainly we don't -- while the white-  
13 to-white doesn't correlate with sulcus-to-sulcus  
14 dimensions, it is highly impractical to do ultrasound  
15 biomicroscopy as 20 or 50 megahertz. It's very  
16 unwieldy. At 50 megahertz you almost can't do it.  
17 You have to make a collage of the pictures in order to  
18 measure it, and I don't think we have anything better.  
19 If something better becomes available, it may be worth  
20 recommending in the future.

21 DR. WEISS: Dr. Macsai.

22 DR. MACSAI: I respectfully disagree with

1 Dr. Sugar, not about ultrasound biomicroscopy, just  
2 about the irreproducibility, if that's a word, of the  
3 caliper method. And that since you need an anterior  
4 chamber depth measurement from the back of the cornea  
5 to the front of the lens, you're getting two for one  
6 there with Orbscan. That's been validated  
7 reproducible.

8 DR. SUGAR: I said measure white-to-white.  
9 You're talking about measuring white-to-white in terms  
10 of what instrument? I didn't say what instrument to  
11 use.

12 DR. MACSAI: Well, I did.

13 DR. SUGAR: That is, you're saying -- I  
14 understand - that Orbscan is a better way to measure  
15 white-to-white. And again, I don't -- I'm not aware  
16 of validation of that information apropos of this  
17 device.

18 DR. MACSAI: Well, then I guess we need to  
19 ask the Sponsor if they used that technique, because  
20 I thought the Sponsor used many techniques. I don't  
21 know if I'm allowed to do that at this time, Madam  
22 Chairperson.

1 DR. WEISS: Not at this time. We can have  
2 them address it in the proper time point, but not at  
3 this point. Does anyone else have any opinions on  
4 that? We're going to get some musical accompaniment  
5 at the same time by Dr. Bradley which is quite kind.  
6 Anyone else have any opinions on this particular  
7 point? No, so I think that is -- does anyone have any  
8 concerns about measuring it with calipers, aside from  
9 those that have been expressed? So we will move on.  
10 I guess for the FDA, I think what's been expressed is  
11 if the Sponsor has shown that Orbscan is any more  
12 accurate than calipers, we would go with that, but I  
13 doubt that's what they've shown, because if they did,  
14 that would have been clearly presented. Malvina.

15 DR. EYDELMAN: The nature of the question  
16 wasn't to try to determine the instrumentation that's  
17 best to perform the measurement with. The question --  
18 during the study, the white-to- white was only  
19 measured with calipers. The Orbscan was used for ACD.  
20 What this question intends to get at is whether the  
21 white-to- white measurement is appropriate for sizing  
22 of the ICL.

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1 DR. WEISS: Well, I think the panel would  
2 probably agree that it may not be great, but we don't  
3 have another option. And nothing else was done in the  
4 study, so we don't have a choice. Would anyone  
5 disagree with me, any of the primary reviewers  
6 disagree with that spin? So the answer is, we think  
7 it's just great, since we have nothing else. We will  
8 go to question 4.

9 DR. EYDELMAN: Did you want me to read it,  
10 or do you want me to just project the question part?

11 DR. WEISS: Why don't we -- can you read  
12 the question part of the question?

13 DR. EYDELMAN: Question 4(a), "Does the  
14 safety and efficacy data for eyes with preoperative  
15 myopia of greater than 15 to 20 diopters support this  
16 range"?

17 DR. WEISS: From what I understood from  
18 all of the primary reviewers, everyone seemed to be in  
19 agreement that it supported this refractive range if  
20 the labeling was changed to reduction of myopia, as  
21 opposed to correction. Dr. Macsai.

22 DR. MACSAI: Maybe I misled you. I didn't

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1 mean that. I think that this is something the Agency  
2 has to provide a guidance document on. I think when  
3 the Agency tells us what are acceptable outcomes in  
4 the minus 15 to minus 20 range, then we can approve  
5 it. But right now, we're throwing the dice. It's  
6 arbitrary.

7 DR. WEISS: Dr. McCulley.

8 DR. MCCULLEY: I have to ask a question of  
9 what the Agency expects of us. If they bring  
10 something to us for an opinion, and they have a  
11 guidance document, then we would apply our opinion, or  
12 use that in our decision making. If they bring  
13 something to us and ask us an opinion where there's  
14 not a guidance, then I think my impression would be  
15 the FDA would be asking us to provide our best opinion  
16 based on what's provided to us.

17 DR. WEISS: You're entirely correct. And  
18 also guidance documents are just that, you don't have  
19 to adhere to guidance documents. They're just meant  
20 as guidance. So with that in mind, Dr. Macsai, what  
21 is your opinion sans guidance document?

22 DR. MACSAI: My opinion from history is

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1 once approved, guidance or no, it's set as a standard  
2 for those that follow. And I urge the panel to  
3 proceed with caution. I think it's arbitrary. I  
4 think the numbers are limited, and I have trouble with  
5 it in this range of myopia because once this is  
6 approved, every other device will be measured compared  
7 to this. Whether appropriate or not, the comparison  
8 will be made.

9 DR. WEISS: I see Dr. Rosenthal shaking  
10 his head, and I think really what we have to do - this  
11 is not a guidance. This is, we have to decide on the  
12 efficacy and safety of this particular device. And  
13 you can have the labeling reflect. So, for example,  
14 as has been suggested by Dr. Sugar, you could say that  
15 this does not -- this is not for correction of entire  
16 myopia in above minus 15, but it's for reduction of  
17 myopia in this group. Dr. Rosenthal.

18 DR. ROSENTHAL: May I just clarify, Dr.  
19 Macsai, that in fact, each Class 3 PMA must stand on  
20 its own, and a decision should be made without  
21 comparison to data from any other PMA. And I think  
22 that's the way -- we've been pretty consistent about

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1 that over the past 7 or 8 years. So hopefully, what  
2 decision you make on this will not bear on another  
3 decision made on another device.

4 DR. WEISS: Dr. McCulley.

5 DR. McCULLEY: My impression is that often  
6 despite guidance to industry, they will try to use  
7 prior PMAs and compare, despite the fact that they're  
8 advised not to do that. We don't have any control  
9 over that. But it really should not set anything that  
10 can be legitimately used in the future in a PMA  
11 application or presentation.

12 DR. WEISS: And also, we've just been, you  
13 know, guided by Dr. Rosenthal, is that we should not  
14 be -- that should not reflect what your opinion is at  
15 this particular point. Your opinion should stand  
16 alone for the devices being brought forward to you.  
17 So with that in mind, without thinking of the future  
18 or the past, just the moment, is this efficacious for  
19 reducing myopia in patients who have more than a minus  
20 15? Dr. Schein, then Dr. McMahon.

21 DR. SCHEIN: Jayne, I hope I don't throw  
22 too much of a wrench in the works, but it seems to me

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1       there's one overriding question that needs to be  
2       addressed before getting into the sub-levels. So  
3       assuming that there's some consensus that there is  
4       efficacy, which I think I've heard some consensus,  
5       there also seems to be some consensus of concern about  
6       certain adverse events.

7                   DR. WEISS: Which we will get into, so  
8       this is --

9                   DR. SCHEIN: Which you cannot separate  
10       this tension between having an appearance of safety  
11       during a short time period, and uncertainty in a long  
12       time period. You can analyze this all day long, and  
13       that uncertainty will still be there. So my entire  
14       focus on these questions has to do with the level of  
15       rigor and detail that one can request in a post market  
16       setting. Everything else depends upon that.

17                   DR. WEISS: Because these are going to be  
18       very -- this is going to be, obviously, a much longer  
19       discussion and much more detailed, I'm trying to get  
20       some of the housekeeping out of the way. I understand  
21       this is not scientific, but on the other hand, I think  
22       it'll work, so I'd ask you to bear with me.

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1 DR. SCHEIN: Okay.

2 DR. WEISS: We may not get to the bottom  
3 line on all these questions, but certainly, once we  
4 start getting involved in the question of what are the  
5 endothelial cell specular microscopy data mean, are we  
6 talking about post-market studies, this is going to be  
7 a more lengthy discussion, and I want to delay that  
8 lengthy discussion.

9 DR. SCHEIN: Okay. So to answer, I'd say  
10 efficacy, yes - safety, unknown.

11 DR. WEISS: Fine. That's good enough.  
12 Dr. Matoba.

13 DR. MATOBA: Then maybe we should do the  
14 first of those questions first, and then come back to  
15 this.

16 DR. WEISS: Well, I'm actually mostly  
17 interested in efficacy, so I think if the answer is it  
18 shows efficacy for reduction, then we have an answer.  
19 And then I think for the question of safety, that's  
20 going to be going across the refractive ranges. Is  
21 there any other discussion on this particular  
22 question? We may need to come back to it.

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1                   SPEAKER: Can you get a sense of the panel  
2 for us?

3                   DR. WEISS: I'm just going to have a hand  
4 show, a brief vote. What -- if the members of the  
5 panel could raise their hand if they believe that this  
6 device is efficacious for reduction of myopia in  
7 patients with refractive errors greater than minus 15.  
8 Those of you who believe it's efficacious, we're not  
9 discussing safety at this moment, can you please raise  
10 your hand.

11                   (Vote taken.)

12                   DR. WEISS: So I think that's --

13                   SPEAKER: Is this a reduction, Jayne?

14                   DR. WEISS: Reduction, yes. I think  
15 that's consensus, so that would answer for efficacy.  
16 I'm going to skip then to Question 6 on IOP rise, if  
17 we could.

18                   DR. EYDELMAN: There was a 4(b), but I was  
19 instructed to skip it.

20                   DR. WEISS: What was 4(b)? I'm sorry.

21                   DR. SUGAR: Corrections to treatment.

22                   DR. WEISS: Well, we did say reduction.

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1 We said reduction of myopia. Question 6 relates to  
2 IOP increase. Would you be able to read that?

3 DR. EYDELMAN: Certainly. "Do you believe  
4 that specific recommendations regarding early  
5 post-operative follow-up are needed in the labeling"?

6 DR. WEISS: So Dr. Macsai has suggested in  
7 relationship to the IOP rise that it be suggested that  
8 the pressure be checked 4 to 6 hours later. Dr. Sugar  
9 suggested that there should be -- the Sponsor should  
10 indicate a better way to assess the size of the  
11 iridotomies when they're too small. Could I have some  
12 discussion on these particular recommendations? Dr.  
13 Macsai.

14 DR. MACSAI: I would also ask maybe Dr.  
15 Coleman to help us with the question of timing of the  
16 iridotomies, if 7 days in advance is the appropriate  
17 amount of time to ensure patency. And then the second  
18 part is, which I forgot to mention in my verbal  
19 review, I did in my written review, is whether or not  
20 irrigation and aspiration of the viscoelastic would be  
21 recommended by the Sponsor, because that's what was  
22 used when the pressure rise was thought to be due to

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1 retained viscoelastic in those problematic cases.

2 DR. WEISS: Dr. Coleman.

3 DR. COLEMAN: This is Dr. Coleman. In  
4 terms of the timing, it's really hard to tell from  
5 their data whether or not the problems that they had  
6 with the iridotomies closing in the post-op period was  
7 because the iridotomies were done within 7 days of the  
8 surgery. They were still on steroids when you look at  
9 the PMA at the time of surgery, so it would be  
10 recommended that they actually had done the  
11 iridotomies at least two to three weeks prior to  
12 surgery, confirmed the patency of the iridotomies  
13 prior to placing the implant. And then also having  
14 the patients off of steroids, because that would  
15 reduce their steroid responders, because they also had  
16 problems in the PMA of individuals that they  
17 identified as having interocular pressure elevations  
18 due to steroid response.

19 And in their labeling, they do have that  
20 irrigating with a 27- gauge cannula to the wound is  
21 sufficient to flush viscoelastic from the eye. I  
22 would say that's not true. Their own data shows that

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1 it's not sufficient, and so you would -- they would  
2 need to change that wording, and also to show in the  
3 labeling that if you don't flush the viscoelastic from  
4 the eye, you can have some major problems with  
5 interocular pressure spikes. So as Dr. Grimmett had  
6 mentioned, IV Diamox may be beneficial in preventing  
7 these.

8 In terms of checking the interocular  
9 pressure afterwards, that would need to be within like  
10 4 to 6 hours of a procedure, and then the following  
11 day they would also need to check it within 24 hours,  
12 and also 48 hours, because they had spikes up to two  
13 days. And it's well known that viscoelastic can  
14 remain in the anterior chamber from 48 to 72 hours, if  
15 it's not flushed out.

16 DR. WEISS: Let me just clarify. You  
17 would then suggest in labeling that it be indicated to  
18 check pressure 4 to 6 hours, and 48 hours. And what  
19 are your time points?

20 DR. MACSAI: I would say 4 to 6, 24, and  
21 48 hours.

22 DR. WEISS: Is that not onerous? We don't

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1 do that with cataract extractions. Dr. McCulley.

2 DR. McCULLEY: The issue is -- I mean, if  
3 you're going to irrigate, as I understand it, the way  
4 the viscoelastic was removed, it's a cohesive  
5 viscoelastic. You tried to irrigate it out with a  
6 27-gauge cannula. Why not use something like a Simcoe  
7 needle for I&A? I mean, I think that's the point.  
8 Then there would be less concern. I still would go  
9 with the 4 to 6 hours, and the 24 hours, but I would  
10 think that would be a better approach.

11 DR. COLEMAN: Because one of the problems  
12 is you get -- this is Dr. Coleman. You get  
13 viscoelastic in the trabecular meshwork, and even  
14 sometimes even irrigating it out, you don't get all  
15 the viscoelastic out in certain eyes. And some of  
16 these eyes are going to be predisposed to having  
17 interocular pressure spikes. Because of the study  
18 design, they were already on steroids, and so that's  
19 predisposing them, in addition to their being myopic.

20 DR. WEISS: How many procedures do we do  
21 that we require patients to come back 4 to 6 hours  
22 later to check if we still have viscoelastic in them?

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1 I mean, I think that's not -- that's fairly burdensome  
2 in my book.

3 DR. COLEMAN: Well, there may -- I think  
4 one of the issues is that if you take eyes that run  
5 and spike pressures up to 55 or 65, and these eyes  
6 are, you know, very painful and stuff, it's an issue  
7 in terms of in the orange study when Dr. Grimmett had  
8 pointed out, where they looked at those 50 eyes. They  
9 actually gave people IV Diamox on the table, and the  
10 4 hours later post-operatively, and they didn't report  
11 any of those acute IOP pressure spikes.

12 DR. WEISS: But if we're talking about  
13 such a small percentage of eyes that are -- in which  
14 that's happening, wouldn't it --

15 DR. COLEMAN: You don't know the long-term  
16 ramifications of elevated interocular pressure spikes  
17 to 65 for 24, 48, 72 hours, even in a young person.

18 DR. WEISS: Dr. Mathers, and then Dr.  
19 McCulley.

20 DR. MATHERS: In common sense terms, I  
21 don't see that this is terribly difficult from filling  
22 an eye with viscoelastic when you do cataract surgery,

1       measure pressure the next day, and if there's a  
2       problem, you continue to measure it. It sounds to me  
3       like this would work if you did that, but I certainly  
4       think it's necessary to measure it the next day. And  
5       if you treat promptly, you perhaps will tolerate, like  
6       cataract surgery patients do, a brief pressure rise.

7                 DR. COLEMAN: This is Dr. Coleman. It's  
8       debatable how brief is 24 hours with a pressure up to  
9       65. And even if you potentially irrigate it, they can  
10      re-spike again. I mean, it's -- we see it in terms of  
11      the management of individuals with cataract surgery,  
12      where we have to go for 48 hours, sometimes managing  
13      pressure spikes. Now these are eyes with compromised  
14      angles, but you don't know how many of these  
15      individuals do have already potentially compromised  
16      angles because we don't really have the gonioscopy on  
17      it. And so it's some -- unfortunately, the issue is  
18      muddied with the viscoelastic, the closed iridotomies,  
19      and then potential problems with the angle due to the  
20      placement of the phakic lens.

21                DR. WEISS: You know, I think on this  
22      particular issue, since it's -- we can agree to

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1 disagree on this particular one, so that has -- the  
2 idea of perhaps suggesting an IOP check in 4 to 6  
3 hours, and 24 hours, and also putting in labeling that  
4 the IOP rise may occur if viscoelastic is not rinsed.  
5 Those have both been suggested. Can you elaborate,  
6 Dr. Sugar, about the labeling advice you would want as  
7 far as the iridotomies go?

8 DR. SUGAR: I will -- well, I need to back  
9 up a little bit. I think that there were only 2 or 3  
10 patients that required re-irrigation of viscoelastic  
11 out of 20 that had pressure elevations that were  
12 substantial. I don't think that's sufficient to  
13 mandate a change in the way you get rid of the  
14 viscoelastic.

15 There's a cost issue if you're going to  
16 have to have a machine to do I&A, and having tubing  
17 and stuff, or even a Simcoe. I don't think there's  
18 sufficient evidence to suggest that the techniques  
19 suggested by the Sponsor should be altered. Your  
20 question was?

21 DR. WEISS: You had mentioned having a  
22 better way to assess the size of the iridotomy when

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1 it's too small.

2 DR. SUGAR: I just wonder if the Sponsors  
3 had from those 17 patients that needed their  
4 iridotomies enlarged, if there was -- you know, if the  
5 distance between them was insufficient and, therefore,  
6 they were covered, or if there was something about  
7 them that would suggest a different approach to doing  
8 the irridotomies to make that less likely to happen.  
9 I certainly think that Anne's suggestion that you do  
10 it longer in advance, and you look and see that  
11 they're patent makes perfect sense.

12 DR. WEISS: So basically, if the Sponsor  
13 could provide information of what they've learned for  
14 those iridotomies that had to be enlarged, what was  
15 done incorrectly the first time around?

16 DR. SUGAR: If they have such information.

17 DR. WEISS: I think unless anyone has more  
18 comments on this question, we'll go to Question number  
19 1.

20 DR. McCULLEY: You've skipped 5. Jayne,  
21 you skipped 5.

22 DR. WEISS: I know. Intentionally.

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1 DR. McCULLEY: Okay.

2 DR. WEISS: Because I was afraid that Dr.  
3 Schein was going to be getting out another wrench.

4 DR. McCULLEY: You pretty much rusted his  
5 wrench.

6 DR. WEISS: I have a feeling it was going  
7 to be headed in my direction, so we'll go to 1. One  
8 is the question which has been sort of the most  
9 emphasized point during the discussion, is about the  
10 significance of the specular microscopy data. And I'm  
11 going to hit a couple of things concerning this  
12 question that maybe we can reach consensus on before  
13 we get to the more contentious issue.

14 Dr. Grimmett and Dr. Macsai both suggested  
15 that a minimal number of cells, specular microscopy be  
16 performed pre-op, and that patients have a minimal  
17 number of endothelial cells before consideration is  
18 made for having this procedure. I'd like to have some  
19 discussion on that by the panel. Is that something  
20 that people agree with or not? Dr. McCulley.

21 DR. McCULLEY: Oh, I was just nodding to  
22 myself.

1 DR. WEISS: That's dangerous around here.

2 DR. McCULLEY: I see. I think that's  
3 reasonable. I think that to screen patients to be  
4 certain that they have normal endothelium for age  
5 prior to the procedure is wise and prudent.

6 DR. WEISS: Dr. Mathers, and then Dr.  
7 Grimmett.

8 DR. MATHERS: Some of the subjects had  
9 very little endothelial counts to begin with, and  
10 that's going to be part of this population if you do  
11 any sizeable number. I think it would be very unwise  
12 to not have some lower cut-off for endothelium. And  
13 I think it's appropriate to look at endothelial cell  
14 counts.

15 DR. WEISS: Dr. Grimmett.

16 DR. GRIMMETT: I agree with Dr. McCulley,  
17 but I would ask Dr. McCulley, would you set your lower  
18 threshold at like one standard deviation, or two  
19 standard deviations lower than a normal mean value for  
20 that given age range, or how would you set your  
21 threshold?

22 DR. McCULLEY: I suppose I'd need -- you,

1 again, have more confidence in these counting things  
2 than I do. I guess I'd want to look at the data for  
3 normal, and for age, and one and two standard  
4 deviations before I would answer that. I would just  
5 leave it loose and for right now that it be normal for  
6 age. And I would think that would add additional  
7 comfort to all of us, and those who are really  
8 concerned about the accuracy and reproducibility of  
9 the density. But I think that would be a reasonable  
10 thing to add, that should give us all more comfort  
11 with this whole issue.

12 DR. GRIMMETT: Dr. Grimmett again. I  
13 agree with Dr. McCulley. I had suggested a year ago  
14 to use age stratified normal means, plus or minus one  
15 standard deviation. But I think that's debatable  
16 exactly where you draw the line. Normal for 20 to 30,  
17 for example, is about 2950 plus or minus 150 or so,  
18 something like that.

19 DR. WEISS: Dr. Macsai had also suggested  
20 in line with this that post-op endothelial cell counts  
21 be done, and consideration of explantation be made if  
22 the cell count is dropping. Is that -- what does the

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1 panel -- Dr. McCulley. You're shaking your head  
2 again.

3 DR. McCULLEY: Again, we don't know --  
4 we're missing so much information. We need to know  
5 what the remodeling process of the endothelial is over  
6 time based on degree of initial injury, surgical  
7 injury, and age of the patient that has incurred the  
8 injury. So I'm not sure that I would know what to say  
9 in terms of when to do it, when not to. I think it  
10 ends up being surgeon judgment to make those  
11 decisions. I don't think we can dictate anything  
12 because we just simply don't know.

13 DR. WEISS: Dr. Sugar, then Dr. Schein.

14 DR. SUGAR: I agree that we don't know,  
15 and that we have no data, you know -- having no reason  
16 to postulate a source of progressive endothelial cell  
17 loss, and having no data on what that second  
18 intervention would do to progressive endothelial cell  
19 loss, I would think that that would be actually the  
20 opposite of the recommendation that I would want to  
21 make.

22 DR. WEISS: Dr. Schein.

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1 DR. SCHEIN: We can make a distinction  
2 between recommending doing a monitoring test and the  
3 timing of an intervention. So by analogy, one might  
4 recommend in a glaucoma setting, visual fields at a  
5 certain frequency without recommending when a  
6 trabeculectomy be done. And I think that there is a  
7 concern about long-term endothelial attrition, it  
8 makes sense to recommend that the only test that we  
9 have be performed on some schedule.

10 DR. SUGAR: But we don't know what  
11 intervention.

12 DR. SCHEIN: Well, no, but we have an  
13 opportunity to, one, learn the natural history. And  
14 the other is to describe to a patient that over the  
15 last five years, you've had a 25 percent loss of  
16 density.

17 DR. WEISS: Dr. Sugar.

18 DR. SUGAR: There's a difference between  
19 recommending that the Sponsor get post-marketing data  
20 on that, and recommending that the practitioner do  
21 that, because we don't get that data. And presumably,  
22 the Sponsor doesn't get that data.

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1 DR. WEISS: Dr. Sugar's point is very  
2 important, and we're going to be getting into whether  
3 there should be any post-market studies, is data that  
4 is interesting shouldn't be put in labeling. That's  
5 up to any of us here or outside to do a study. But  
6 data that would be important, we feel, for patient  
7 care, should be put in the labeling. So is the  
8 specular microscopy post-operatively important for  
9 patient care? And Dr. Sugar would disagree. Dr.  
10 Mathers.

11 DR. MATHERS: I would agree that it is  
12 important to patient care. There are some patients  
13 here that had very substantial loss in cell count, and  
14 you would want to pick those up. And it would be  
15 important for that patient's well-being that you do so  
16 at some not short interval after surgery, perhaps a  
17 year or something like that.

18 DR. WEISS: So if you're going to give  
19 guidance as far as when repeat specular microscopy  
20 would be done, what would you suggest?

21 DR. MATHERS: As early as three months,  
22 possibly six, and at latest, one year.

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1 DR. WEISS: Somewhere between six months  
2 and a year. Dr. Macsai.

3 DR. MACSAI: That's not what I intended by  
4 my comment.

5 DR. WEISS: What did you intend?

6 DR. MACSAI: My intention was that in my  
7 hands and my practice, if I was to implant this  
8 device, which appears to be an efficacious device, we  
9 don't have an answer about the long-term endothelial  
10 damage. And I, as alluded to by both Dr. Sugar,  
11 Schein and Mathers, would want to know if my patient  
12 was getting into trouble. And if they go from 28 to  
13 2000, there's trouble right here in River City, and  
14 it's time to decide if that thing is safer in or out.  
15 And I don't want to wait until there's microcystic  
16 edema and we're transplanting that cornea in a 4 year  
17 old.

18 DR. WEISS: What do you recommend for  
19 labeling though? This is what you do when --

20 DR. MACSAI: I want to suggest --

21 DR. WEISS: You suggest, okay.

22 DR. MACSAI: -- that the practitioner

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1 follow their patients with endothelial cell counts,  
2 because that's all we have.

3 SPEAKER: For what time?

4 DR. MACSAI: Well, my personal opinion, I  
5 would say five years. And when we got all this  
6 long-term data that comes in, and it shows that I'm  
7 off the wall, I'll be the first to stand up and say  
8 thank you. I'm wrong, and then we can change the  
9 labeling on the device, and that will be a wonderful  
10 thing.

11 DR. WEISS: Well, actually, you know, we  
12 don't even have to --

13 DR. MACSAI: Annually for five years.

14 SPEAKER: Oh, annually.

15 DR. MACSAI: Is that what you want?

16 DR. WEISS: And actually, we don't even  
17 have to -- and I'll defer to Dr. Rosenthal. We could  
18 just say if this was what we're trying to --  
19 everything is a suggestion here. Even our vote is a  
20 suggestion. We could say that --

21 DR. ROSENTHAL: If you suggest that you  
22 put it in labeling as a suggestion, you put doctors in

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1 liability risk if they don't do it. So if it's in the  
2 labeling, and it's not done, even as a suggestion, I  
3 think it holds greater water than a suggestion.

4 DR. WEISS: So you might be suggesting to  
5 the malpractice attorney to take that case.

6 DR. ROSENTHAL: Did I make myself clear?

7 DR. WEISS: Malvina.

8 SPEAKER: You put people at medical legal  
9 risk.

10 DR. WEISS: Yeah. Did you want to  
11 comment? No. Dr. Sugar and Dr. McMahon.

12 DR. ROSENTHAL: Excuse me. So therefore,  
13 I think what you put in as a suggestion will be done.

14 SPEAKER: That will just be a suggestion,  
15 maybe wrong.

16 DR. WEISS: Dr. Sugar and then --

17 DR. SUGAR: To use Mike Grimmett's term  
18 arguendo, to play devil's advocate, we don't know what  
19 to do with that information. I think that it is  
20 appropriate in the labeling to suggest that  
21 practitioners monitor corneal health subsequent to the  
22 procedure, period, and to deal with however you see

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1 fit. We do not have any information that I am aware  
2 of that suggests that knowing that the cell count is  
3 now 1200, and it was 2000 eight months ago, that any  
4 intervention that we're going to do is going to alter  
5 that state. So how could we make a recommendation  
6 that you gather that information so that you can alter  
7 that state, when you don't know how to do it? That's  
8 -- my point is that if you go in and take the IOL out,  
9 my suspicion is you're going to lose more endothelial  
10 cells. You're not going to help the situation.

11 DR. WEISS: Well, you could say that  
12 physicians should monitor the corneal health with such  
13 means as A, B, C, or D, and include this as the  
14 possibilities.

15 DR. SUGAR: I think that as Ralph  
16 suggested, the more specific we get, the more we  
17 constrain the practitioner.

18 DR. WEISS: Dr. Ho.

19 DR. HO: Furthermore, just as a retinal  
20 surgeon, give me a sense for what percentage of  
21 anterior segment surgeons have or do specular  
22 microscopy. Is this something that is routine?

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1 SPEAKER: Yes. Routine.

2 SPEAKER: yeah.

3 DR. HO: Routine for all cataract  
4 surgeons? Okay.

5 DR. SUGAR: No, it is not. No, he's  
6 talking about the average doctor --

7 DR. WEISS: Dr. Macsai.

8 DR. MACSAI: When it was reimbursable --

9 DR. WEISS: Dr. Macsai.

10 DR. MACSAI: I'm going to tell you when it  
11 was reimbursable it was routine, so that the access to  
12 it, I think, remains.

13 DR. HO: Furthermore --

14 DR. WEISS: How about let's tell you who  
15 -- Dr. Ho. Yes.

16 DR. HO: But I suspect that this  
17 procedure, were it to be approved, would be something  
18 that would be done by comprehensive ophthalmologists,  
19 as well.

20 DR. WEISS: Dr. McCulley.

21 DR. McCULLEY: From a practical  
22 standpoint, there are a couple of issues here. One,

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1 we've already said we thought that a person should  
2 have pre-op specular microscopy. Number two, most  
3 people who are active in these areas are going to have  
4 a specular microscope then to do it post-op. And if  
5 not, it's available in the community, so I don't think  
6 we'll be limiting the market scope or the number of  
7 people doing this if we require specular microscopy.  
8 On the other hand we did, we required high frequency  
9 ultrasonography, we might. But with specular  
10 microscopy, I don't think it's going to have a  
11 negative impact or be unfair to have it pre-op. But  
12 whether we do make a specific suggestion about it  
13 post-op or not, I feel less strongly about. I kind of  
14 lean toward Joel, that we need to -- if I interpreted  
15 Joel correctly, we need to leave that to the judgment  
16 of the physician. And then if we want a post-market  
17 study, then rather than suggesting that every  
18 ophthalmologist do it, that we request a post-market  
19 surveillance study on endothelial cell count.

20 DR. WEISS: So I'd just like a poll at  
21 this point in terms of how the panel views this  
22 question. Those who would be in favor of suggesting

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1 or mandating, or indicating in the labeling that  
2 endothelial cell counts not only be performed  
3 preoperatively, but also be performed  
4 post-operatively, and we don't even have to indicate  
5 at what time point. Those of you who would like them  
6 performed post-operatively in the labeling, could you  
7 please raise your hand.

8 (Vote taken.)

9 DR. WEISS: So we're almost split down the  
10 middle on that, so that issue is not decided at this  
11 moment. Yes, Dr. McMahon.

12 DR. McMAHON: We're getting into a  
13 circular argument here. And we don't have the data to  
14 know what's happening with the endothelium, so making  
15 suggestions to the Sponsors and practitioners is not  
16 -- it's more emotional than logical. And my  
17 suggestion is, is that we get the information from the  
18 sponsor so that you can then address the labeling  
19 question, which goes to a post-market study, which  
20 goes to Dr. Grimmatt's seeing year four and year five  
21 data. And actually, directing to this question, the  
22 answer is have we showed stability? The answer, I

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1 think, is no, they haven't shown anything yet. The  
2 second part of the question is, is how many eyes and  
3 for how long? And I think we should decide.

4 DR. WEISS: We will in a moment. I want  
5 to get to the more difficult stuff, and just get the  
6 simpler things out of the way. The anterior chamber  
7 depth cut-off of 3, should this -- would you be able  
8 to read that portion of the question?

9 DR. EYDELMAN: "Do the outcomes of the  
10 endothelial cell density analysis provide reasonable  
11 assurance of safety for this device for eyes with 1  
12 ACD of 2.8 to 3, and 2 ACD of greater than 3  
13 millimeters."

14 DR. WEISS: And all the primary reviewers,  
15 Dr. Sugar, Dr. Macsai, Dr. Grimmett, all suggested  
16 that this not be implanted in ACDs less than 3. Is  
17 there any discussion on that from the panel? Dr.  
18 Bradley.

19 DR. BRADLEY: Dr. Gray, in his statistical  
20 presentation, showed no evidence that there was a  
21 dichotomizing of the data. You did a linear model to  
22 fit all of the data, and I queried Dr. Gray on how

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1 much of the variance is explained by this linear  
2 model. It looked to me like not much of it. And,  
3 therefore, I wonder about making judgments about a  
4 certain threshold level of anterior chamber depth  
5 based upon that study. It didn't seem to me that that  
6 was warranted. I wondered why one of the proponents  
7 of this dichotomy would argue this case, and maybe Dr.  
8 Gray could comment on it.

9 DR. WEISS: Any proponents want to argue  
10 this case? Dr. Sugar.

11 DR. SUGAR: Your point is, you know, the  
12 data, I think, does show that there is a linear, an  
13 apparent linear relationship between anterior chamber  
14 depth and endothelial cell loss. And the only  
15 question is, is there a point where we should cut it  
16 off because there is no obvious dichotomy, an obvious  
17 point to cut it off. Is that correct?

18 DR. BRADLEY: Two points, yeah. One is  
19 that there is no dichotomy in the data themselves.  
20 And the other point is that this is a mean linear  
21 regression, and the data were highly variable around  
22 that point. And it looked like some other factor was

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1 the -- or factors were the primary determiner of cell  
2 death, or cell loss, not the anterior chamber depth.

3 DR. WEISS: Dr. Eydelman, I think, has a  
4 comment.

5 DR. EYDELMAN: We actually -- well, the  
6 Sponsor has actually ran several analyses, and there  
7 were no apparent other factors associated other than  
8 anterior chamber depth. And if I may comment on your  
9 earlier statement; yes, you're correct, from Dr.  
10 Gray's model, it is a linear association.

11 One must keep in mind, however, that as we  
12 progress up that line, the percentage of the overall  
13 population was that ACD depth is going to increase,  
14 i.e., we know that below 3 there's only 5.5 percent of  
15 the overall cohort. And when we get up to 3.5, we're  
16 close to 50 percent of the cohort. So while it's  
17 possible that this line could be drawn somewhere  
18 higher, just keep in mind that then you would be  
19 excluding a higher percentage of patients from having  
20 the surgery.

21 DR. WEISS: Dr. Bradley.

22 DR. BRADLEY: Just an interpretational

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1 point. What you said is correct. It's important  
2 though to realize that with such an exclusionary  
3 criterion, you would be excluding candidates from the  
4 procedure who would have a much smaller level of cell  
5 loss. And you would be including patients who would  
6 have a much larger level of cell loss, simply because  
7 of the variability in that population. And that was  
8 the question I was asking Dr. Gray about, because it  
9 seemed there was so much variability in that  
10 regression analysis. He's nodding his head there, so  
11 perhaps he could --

12 DR. WEISS: Dr. Gray, did you want to  
13 address this?

14 DR. GRAY: Well, the question you asked me  
15 was how much of the variability was explainable by  
16 ACD. And unfortunately, I don't have that with me.  
17 But you are correct, the relationship appeared to be  
18 linear without an obvious break, and there is a fair  
19 amount of spread around the line. But the decision  
20 about where, if at all, to put a cut point on the ACD  
21 is purely a judgment call at this point, I'd say.

22 DR. WEISS: Dr. Grimmett.

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1 DR. GRIMMETT: I was in agreement with  
2 making the cut-off 2.8 to 3 for three reasons. One,  
3 the data on that arbitrary break point showed 50  
4 percent higher loss with a shallow depth. Number two,  
5 the cut-off would not be overly onerous, only 5-1/2  
6 percent of the cohort would be taken out. Number  
7 three, my review of the literature back last year at  
8 our guidance discussion showed that the closer that  
9 phakic IOLs are -- the closer they are to the  
10 endothelium, the greater risk to the endothelium with  
11 angle supported having a higher risk than high risk  
12 clip versus posterior chamber. So I was using all  
13 three in combination just to make that determination.

14 DR. WEISS: Aside from Dr. Bradley, does  
15 anyone else have any concerns about limiting it? Dr.  
16 Bandeen-Roche and then Dr. McCulley.

17 DR. BANDEEN-ROCHE: Yes. I have two  
18 comments. First, I agree with Dr. McMahon that the  
19 primary point, as far as I'm concerned, is whether  
20 stability has, in fact, been achieved. And, you know,  
21 I am not at all convinced that it has been, so at that  
22 point, the distinction between 2.8 to 3, versus 3 and

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1 above, I think is totally arbitrary.

2 The second point just goes back to a point  
3 that Dr. Bradley was making about what else might have  
4 explained the variance. And I wanted to ask Dr. Gray  
5 were you able to reproduce, or did you even try to  
6 reproduce the sponsor's analysis of what were the  
7 factors related to cell loss, and finding only ACD  
8 being the only thing that was related?

9 DR. GRAY: Well, that's a hard question to  
10 answer.

11 DR. BANDEEN-ROCHE: Sorry.

12 DR. GRAY: There's a -- we had a fairly  
13 complicated situation in terms of the data because we  
14 had multiple measurements per person over time. We  
15 have baselines, and there's a lot of missing data.  
16 It's difficult to know how to actually model it. The  
17 Sponsor went through a particular procedure where they  
18 cut up -- they binned the data into categories, and  
19 they checked quite a number of potential co-variates,  
20 and the only one that ended up to be significant was  
21 the anterior chamber depth.

22 If you do some alternative analyses using

1 things like the percent of hexagonal cells at  
2 baseline, or the endothelial cell density at baseline,  
3 sometimes those show up to be significant predictors.  
4 It's not obvious how to, for an individual patient  
5 though, say whether they are at high or low risk of  
6 having a high rate of endothelial cell loss. That's  
7 a very difficult procedure which we didn't go through,  
8 and that would take some amount of effort on  
9 everyone's part to do that.

10 DR. BANDEEN-ROCHE: Thank you.

11 DR. WEISS: Dr. McCulley.

12 DR. McCULLEY: My comment was with Mike.  
13 I don't think it's so much the distance, necessarily,  
14 as how you're fixating it. So you're taking AC  
15 versus, you know, a posterior chamber. I think it's  
16 apt to be more influenced by the way you're fixating  
17 than the distance, except for possibly surgical  
18 trauma. If you've got a bigger space to work in, less  
19 problems - smaller space to work in, more damage. But  
20 I'm not convinced that just the distance -- if you  
21 start throwing in, and try to extrapolate that, the AC  
22 to iris to PC, that that holds up. It's apples and

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1 oranges, and grapefruits.

2 DR. GRIMMETT: Mike Grimmett. Certainly  
3 with the angle supported lens data, there were some  
4 minimum distances that had some very unacceptable  
5 rates of endothelial cell loss for the angle supported  
6 data in and of itself. And grant it, some patients  
7 are eye- rubbers, which would deform the cornea, touch  
8 the edge of the IOL. So certainly for the anterior  
9 chamber at the angle supported phakic IOLs, I think  
10 there's a very strong argument that the closer that  
11 the optic is to the endothelium, the higher the rate  
12 of endothelial cell loss.

13 Now, obviously, trying to translate that  
14 to all three groups with some meta-analysis,  
15 obviously, you get fairly sticky in that. But at  
16 least in that one group, I think the data is fairly  
17 strong.

18 DR. WEISS: Dr. McCulley.

19 DR. McCULLEY: You'd have to keep it  
20 within the category of lens type, fixation type.

21 DR. GRIMMETT: Anyway, enough.

22 DR. WEISS: Just a -- I think we're at the

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1 point that panel members are calling for time out.  
2 That definitely means we've belabored that one. But  
3 I'm not sure we have a consensus on that, but I guess  
4 we will go to --

5 DR. ROSENTHAL: Vote.

6 DR. WEISS: It doesn't actually really  
7 matter if we have a consensus on it or not.

8 DR. ROSENTHAL: It helps the FDA. It  
9 helps us a lot.

10 DR. WEISS: At this point?

11 DR. ROSENTHAL: It depends what you  
12 ultimately say, but we need - -

13 DR. WEISS: Well, do you want the  
14 consensus right now?

15 DR. ROSENTHAL: Yeah.

16 DR. WEISS: Fine. Let's have -- okay.  
17 For those of you who want to limit it, please vote  
18 that you'd like to limit it to 3 and above anterior  
19 chamber depth.

20 DR. EYDELMAN: It's actually above 3.

21 DR. WEISS: Above 3.

22 (Vote taken.)

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1 DR. WEISS: Okay. So I guess we do have  
2 a fairly good consensus. We're going to -- if you  
3 could read Question 1(a).

4 DR. EYDELMAN: I guess I'll read the whole  
5 thing. "The main change between 3 and 4 years in 57  
6 eyes was a gain of .1. A decrease in co-efficient  
7 variation and increasing percentage of hexagonality  
8 were observed. Is there sufficient data to support  
9 the Sponsor's conclusion that the losses in the first  
10 three years are reflective of the surgical trauma was  
11 a prolonged remodeling culminating in stabilization of  
12 cell loss after three years."

13 DR. WEISS: And I'm going to just cut the  
14 question off there. We spent quite a bit of time  
15 having the data presented to us in different formats,  
16 showing us the impressions of this, so I don't know  
17 that we have to discuss this. But I would like to get  
18 an impression of the panel's opinion on this  
19 particular one by vote. And for those of you who  
20 agree there's sufficient data to support the Sponsor's  
21 conclusion that there is stabilization of cell loss  
22 after three years, for those of you who agree with

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1 that statement, can you raise your hand.

2 (Vote taken.)

3 DR. WEISS: So what I can see is that no  
4 one on the panel believes that there is a  
5 stabilization of cell loss -- that the data support  
6 that there is necessarily -- well, why don't you  
7 phrase it, Dr. McCulley.

8 DR. McCULLEY: Well, I mean, your question  
9 was -- we don't know. The question was, do we agree  
10 the Sponsor has presented data that assures us that  
11 there's stabilization after three years. We don't  
12 have that data.

13 DR. WEISS: Fine.

14 DR. McCULLEY: We have an opinion, but  
15 it's opinion based on things, not based on data. I  
16 like to base it on data.

17 DR. WEISS: That's fine.

18 DR. McCULLEY: We don't have data to  
19 support that.

20 DR. WEISS: So we do not have any data --

21 DR. McCULLEY: Up to three years, and then  
22 we can argue the three to four years.

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1 DR. WEISS: Okay. We do not have data  
2 showing that there is stabilization at that period of  
3 time.

4 DR. EYDELMAN: So what is the minimum  
5 number of eyes, and the minimum length of follow-up  
6 that you recommend for this assessment?

7 DR. WEISS: And what this is getting to,  
8 I think is, in order to get this information, are we  
9 talking about any --

10 DR. BRADLEY: Let Karen answer that.

11 DR. WEISS: Well, are we talking about any  
12 further studies, longer studies? Dr. Bandeen-Roche.

13 DR. BANDEEN-ROCHE: Yeah. I mean, I would  
14 consider it entirely a question of a minimum number.  
15 I mean, if you're looking for a number to establish a  
16 power, I mean, I would hope that you would at least  
17 try to establish power to ensure a rate of decline  
18 less than something, or a precision to establish what  
19 the post three year rate of decline is.

20 I would also encourage you not to only  
21 focus on the mean, as Dr. Grimmett has raised; that  
22 it's also important to think about what are the

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1 proportion who are declining at an unacceptable rate.  
2 And so one could do power calculations or precision  
3 calculations to establish a number sufficient for that  
4 quantity. But it does also go to representativeness  
5 of the cohort, you know. And so that's certainly  
6 unlaying my question about how many providers was it.  
7 You know, I would be totally less convinced about the  
8 quality of the data if it was the one or two best  
9 surgeons who had provided the 67 eyes. It sounds like  
10 it was not, that that was not the case. But I don't  
11 have any feel for how representative the 67 eyes that  
12 we have are. And, moreover, if I look at Dr. Gray's  
13 data, one thing that I have been worried about was  
14 regression to the mean. And so, for instance, if the  
15 eyes that are contributing to that 3 to 4 year, the 57  
16 eyes, I guess, 3 to 4 year interval were those who had  
17 declined, you know, particularly far from 2 to 3, or  
18 were particularly low. Then one could expect somewhat  
19 of an improvement just due to regression to the mean,  
20 let alone things like contact lenses and issues like  
21 that. And so, indeed, according to Dr. Gray's table,  
22 all visits, the cohort of 37 has a mean cell count,

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1 100 cells less than all of the other eyes at three  
2 years. So that is in the direction of that concern.

3 And I guess a final point that I would  
4 make would be everyone has been commenting that we're  
5 in a gray zone, that the physicians who participated  
6 in this study were the best of the best. And so I  
7 would not at all just settle for a 95 percent  
8 confidence found, you know, just barely squeaking in  
9 there at a level of a 95 percent confidence found. I  
10 think that I would recommend a bit more assurance than  
11 that, taking into account the fact that this is a  
12 precedent, that these are the best physicians who  
13 participated in this study.

14 DR. WEISS: I think we have to be careful  
15 about this best physicians talking about lack of data.  
16 I'm sure these were good docs and good surgeons, but  
17 creating this extra god-like category, I think we  
18 should take out of the discussion.

19 DR. BANDEEN-ROCHE: That's a point  
20 well-taken. That's a point well-taken. Nonetheless,  
21 I mean, we hardly expect better performance in the  
22 field than we do in a clinical trial.

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1 DR. McCULLEY: You don't have data to  
2 support that statement, do you? Do you have data to  
3 support that statement? You do. Okay.

4 DR. ROSENTHAL: With all kinds of devices.

5 DR. McCULLEY: All right.

6 DR. WEISS: What I would then like to lead  
7 to is since there's agreement --

8 DR. ROSENTHAL: Wait.

9 DR. WEISS: Yes.

10 DR. ROSENTHAL: I want to make sure I said  
11 the right thing. Once they go out in the field, they  
12 tend to have more problems than they do within the  
13 clinical trial.

14 DR. McCULLEY: But you don't have data to  
15 support that the people who do the trials are the best  
16 of the best.

17 DR. ROSENTHAL: No.

18 DR. McCULLEY: I think that is opinion --

19 DR. MACSAI: That's my opinion.

20 DR. McCULLEY: That is Marian's opinion,  
21 and it should not be in our discussions.

22 DR. WEISS: So we're going to take out the

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1 "god" factor out of the discussion.

2 (Laughter.)

3 DR. WEISS: But what I would like to  
4 introduce into the discussion is the fact that since  
5 there is consensus that there's no data demonstrating  
6 stabilization of cell loss between 3 and 4 years, what  
7 would please the panel to do perhaps to demonstrate  
8 that the issue of endothelial cell damage is not  
9 present here? Dr. McCulley.

10 DR. McCULLEY: Yeah. My impression that  
11 we -- I could not argue the point and present data to  
12 absolutely support that we have stabilization. My  
13 impression of everything presented is I would lean  
14 toward we probably do. At least -- or that we  
15 probably will. At least to the point where I would be  
16 comfortable not voting on this, that if the panel  
17 recommended approvable, that I would be comfortable  
18 with that, with some form of continued surveillance or  
19 gathering of data about the stability or lack thereof  
20 of the endothelium.

21 DR. WEISS: Okay. So if we're talking  
22 about post-market study, would we be talking about a

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1 post-market study following the initial cohort, or  
2 would we be talking about -- and would we require  
3 those patients who have had preoperative endothelial  
4 cell counts, or would we be talking about getting a  
5 new cohort with specified time points at which they've  
6 had endothelial cell counts? Dr. Schein, and then Dr.  
7 Sugar, then Dr. Mathers.

8 DR. SCHEIN: I would argue that one needs  
9 both, but for different reasons. So on the specific  
10 question of the data related to the endothelial cell  
11 count, the existing cohort will tell us a lot more  
12 about the natural history. I mean, if there's a three  
13 year lead time on any new cases that come along.

14 On the other hand, when I use the word  
15 "post-market surveillance", it doesn't at all mean a  
16 continuation of a pre-market cohort, because the  
17 question from a public health perspective is very  
18 different. And what you're worried about is a  
19 situation, which I think we have here, where you've  
20 got reasonable short-term safety, and some -- an  
21 inclination - if I could speak generally, you know, to  
22 approve based on that, but concern about longer-term

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1 issues which cannot be addressed from this particular  
2 pre-market cohort.

3 It's an analogous situation with the  
4 extended wear contact lenses, which is currently  
5 undergoing a 5,000 person study looking just for  
6 ulcerative keratitis. So the concerns here are not  
7 just adequate length of follow-up for endothelial cell  
8 count, but the representativeness. We don't have to  
9 get into the glorified surgical skill, but there are  
10 means of examples where you go from an efficacy study  
11 pre-market, to an effectiveness evaluation, which is  
12 how the product is actually used once it's approved.  
13 And it never performs as well. So one needs some kind  
14 of way to sample cases from a post-market setting,  
15 from surgeons and different kinds of patients, to look  
16 at big outcomes; corneal failure, new treatment for  
17 glaucoma, retinal detachment, and cataract, because  
18 there has been some concern in my mind about some of  
19 these other complications, which have all been  
20 reported on a per-eye basis; whereas, obviously,  
21 retinal detachment is a per-patient issue.

22 DR. WEISS: Can you tell me the study --

1 the number of patients, numbers of years that you  
2 would suggest if we're just actually going to make it  
3 concrete? What would you like?

4 DR. McCULLEY: For which purpose?

5 DR. WEISS: For both.

6 DR. McCULLEY: No, I'd have to do some  
7 sample size calculations.

8 DR. WEISS: So you would like --

9 DR. McCULLEY: But even this is, you know,  
10 done in a few hours.

11 DR. WEISS: But you would like, basically,  
12 both types of studies getting a new cohort of patients  
13 with specular microscopy prior to the procedure, and  
14 then following them through, as well as following  
15 these patients?

16 DR. McCULLEY: No. No. So for the  
17 specular microscopy, I would go with the existing  
18 group, because in a post-market surveillance study  
19 that I'm more concerned about, I want to know about  
20 corneal graft. I want to know about retinal  
21 detachment, because the absence of a control group  
22 here is a major deficiency. And, you know, using

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1 control groups based on other case series is  
2 inadequate, so I would like to know on a much larger  
3 sample, with less defined testing, less onerous  
4 testing, about major outcomes; cataract surgery, new  
5 treatment for glaucoma, retinal detachment.

6 DR. WEISS: And how long out would you  
7 follow those patients?

8 DR. McCULLEY: Probably -- initially about  
9 probably 3 to 5 years.

10 DR. WEISS: Do you think for -- I mean,  
11 say those posterior keratotomy took 20 years for them  
12 to get corneal edema, so will that --

13 DR. McCULLEY: Well, each one of these  
14 things is different, so ones that occurred in my  
15 lifetime, professional lifetime. One example would be  
16 extended wear contact lenses, approved for 30 days in  
17 1981. They were reduced in 1989, so about 8 years  
18 later, with a very, very inefficient way of making  
19 that determination. Anterior chamber lenses was even  
20 more inefficient. There was no surveillance  
21 mechanism. There was a lot of controversy about what  
22 we're seeing. The literature is a very inefficient

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1 way to do post- market surveillance. There are many,  
2 many patients who have rigid anterior chamber lenses  
3 with no clinical inclination that one could see as one  
4 followed them.

5 DR. WEISS: Well, we're going to make this  
6 efficient.

7 DR. McCULLEY: Right.

8 DR. WEISS: So for this particular  
9 efficient way of doing it, how long of a follow-up  
10 would you recommend? Would you still say 3 to 5  
11 years?

12 DR. McCULLEY: Yes.

13 DR. WEISS: Okay. Dr. Mathers.

14 DR. MATHERS: In terms of modeling,  
15 addressing what Karen Bandeen-Roche said, I think we  
16 could reasonably have an objective as we model this,  
17 that we would like to stay above. And I think from  
18 our various analyses here, that it is reasonable to  
19 propose that at the end of the expected use of the  
20 device, that we end up with an endothelial cell count  
21 of 1500 or greater, because this is still far less  
22 than the normal cell loss.

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1           Normal cell loss is quoted here as being  
2           .6, but if you do the numbers on the data from Dr.  
3           Grimmett, the normal is really like .4 percent per  
4           year. And if we have a loss rate that you're  
5           calculating of 1, 1.1, we are still like three times  
6           greater than the normal. So if we do our projections  
7           and model this to keep above 1500 by the end of the  
8           device use, I think we will be serving the public  
9           reasonably well. And it's still a relatively  
10          conservative approach.

11           DR. WEISS: So are you saying take the  
12          original cohort and if the cell count kept on dropping  
13          off, at what point, how many years they would take --

14           DR. MATHERS: As this gets modeled and we  
15          have more data, the model is going to get better. The  
16          projections are going to get better, and the width of  
17          -- or the data is going to get more accurate. And as  
18          we can determine this, when we know how accurate it  
19          is, if we set the parameter to keep the end point at  
20          greater than 1500, which we will be able to do as you  
21          continue to model it.

22           DR. WEISS: So you're basically saying to

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1 the FDA that statistically they should try to predict  
2 into the future, and that will tell them how long that  
3 they would be able to do the study. And if that's --  
4 if I'm correct, I'm being told at the same time that  
5 that can't be done.

6 DR. MATHERS: Well, as we get more data,  
7 we don't know how good the data is going to be when it  
8 comes in, and it may be possible in a year or two to  
9 determine what the rate of this loss is.

10 DR. WEISS: I think we probably have to  
11 tell them up front what we want, as opposed to let  
12 this go on for as long as we see fit. Dr. Macsai.

13 DR. MACSAI: I'm a little lost here in  
14 this conversation, and I just want to -- reel me back  
15 in here. I'm listening to what Dr. Schein is saying,  
16 and I'm in no way disagreeing with you, that it would  
17 be interesting to know this information from a public  
18 health perspective. I'm not sure it's the Sponsor's  
19 responsibility to get that data. It would require a  
20 National Registry akin to the Australian Graft  
21 Registry, and I don't know that we have that set up in  
22 the United States.

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1 I think it's a wonderful concept if we  
2 could do it. We have to register every patient that  
3 has this device, and follow them forever, and I'd love  
4 to know. And I just don't know that it's reasonable  
5 to know. So to the second thing, though --

6 DR. WEISS: Actually, he was saying 3 to  
7 5 years.

8 DR. MACSAI: Well, we'd look at them for  
9 3 to 5 years.

10 DR. WEISS: Okay. So you would prefer not  
11 to have a new cohort - -

12 DR. MACSAI: I know about the cataracts,  
13 and I know about the retinal detachments. Okay. But  
14 I thought we were supposed to be talking about the  
15 endothelium here. And I thought the question was how  
16 many patients do we have to follow and for how long to  
17 establish stability of the endothelial cell change,  
18 because we're all setting around not raising our  
19 hands, because we don't know if the endothelial cells  
20 are decreasing to a stable level, so the question is  
21 how many.

22 My answer to you in my review was, I am

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1 not a biostatistician. Dr. Gray is a biostatistician.  
2 Dr. Edelhauser is an expert in endothelium, you know.  
3 Put those two in a room, figure it out, tell us the  
4 answer, we're done.

5 DR. WEISS: Dr. Edelhauser is about to  
6 tell us the answer. Sometimes you get what you want.

7 DR. EYDELMAN: If you're not ready to give  
8 us the exact number, maybe you can give us the  
9 parameters on which to base the calculation, so we can  
10 certainly perform the calculations. But if you tell  
11 us the rate that you'd like to ascertain, and with  
12 which predictability, or with which -- what  
13 statistical parameters you want us to include, we can  
14 certainly perform the calculations.

15 DR. WEISS: Well, let me just get one  
16 thing from the panel, just in terms of following the  
17 initial cohort. Whether it's those 200 - - one  
18 question for the panel. For this cohort that would be  
19 looked at with specular microscopy, does the panel  
20 want these patients to have had pre-operative specular  
21 microscopy done? Those of you who would like to have  
22 at least pre-operative specular microscopy, could you

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1 raise your hand.

2 (Vote taken.)

3 DR. WEISS: So I think there's -- Dr.  
4 McMahon. There's a majority that would like  
5 pre-operative specular microscopy. So from what I  
6 recall from the FDA's presentation, there were 206  
7 patients who had pre-operative specular microscopy,  
8 and at least two time points afterwards. Correct me  
9 if I'm wrong. So of those 206 patients, perhaps we're  
10 starting out that with -- that's the maximum number.  
11 And then we could -- we'll probably go down from that.

12 Does the panel think that 206 would,  
13 starting out, be too low? Would it be feasible to tap  
14 into that population? Anyone have an opinion on that?  
15 Dr. Macsai.

16 DR. MACSAI: I think that's the only  
17 population we have. I think we expect a 10 percent  
18 loss to follow-up. You know, unfortunately those 206  
19 weren't told you've got to come back every year for  
20 five years. So the Sponsor, I'm sure, will do their  
21 best to track them down and reel them in, and look at  
22 their endothelium. And whether or not it's

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1 statistically significant, Dr. Gray will tell us.

2 DR. WEISS: So then I would propose that  
3 that 206 could be at least the cohort that we're  
4 looking at for a post-market study. Then the second  
5 question that the FDA has asked us and I will ask the  
6 panel, is there guidance for number of years that you  
7 would like these people followed? Dr. McCulley.

8 DR. McCULLEY: I think five is reasonable.

9 DR. WEISS: An additional five years?

10 DR. McCULLEY: No.

11 DR. WEISS: Total of five years.

12 DR. McCULLEY: Total of five years.

13 DR. WEISS: So that you want one more time  
14 line at one year down the line.

15 DR. McCULLEY: No. What I want -- what I  
16 would ideally like to see, again, I have a sense that  
17 all we've done is shift the things to the right or  
18 left, however you're looking at it. But I would like  
19 to see yearly up to five years for as many years as  
20 possible. We've already missed some years for that  
21 cohort of 206.

22 DR. WEISS: Okay. Well, those -- okay.

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1 Dr. Sugar.

2 DR. SUGAR: I was going to say the same  
3 thing. The last patient -- the first patient should  
4 reach the five year time window next month. And the  
5 last patient would reach that time in December of  
6 2007, so I think as many patients as possible should  
7 get -- of those 306, not 206. There are 306 that had  
8 baseline specular microscopy. As many of those as  
9 possible should get annual data for as long as -- up  
10 to as many --

11 DR. WEISS: Dr. Eydelman, would that  
12 answer 1(a)?

13 DR. EYDELMAN: So you want all eyes in the  
14 PMA cohort that had pre-operative endothelial cell  
15 counts to be followed for five years. Is that  
16 correct?

17 DR. SUGAR: With specular microscopy.

18 DR. WEISS: Dr. Sugar, is that correct?

19 DR. SUGAR: That's what I'm suggesting.

20 Yes.

21 DR. WEISS: That's correct. Dr. McCulley,  
22 you concur?

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1 DR. McCULLEY: I think that's reasonable,  
2 annually for five years.

3 DR. WEISS: Is that -- Dr. Rosenthal, is  
4 that burdensome?

5 DR. ROSENTHAL: No, but we need to know  
6 whether you want it done in the pre-market arena, or  
7 in the post-market arena.

8 DR. McCULLEY: Post.

9 DR. WEISS: Post-market arena is what Dr.  
10 McCulley.

11 DR. McCULLEY: It depends on whether you  
12 approve it now or not.

13 DR. WEISS: Dr. Sugar, post-market arena?

14 DR. SUGAR: Yes. I mean --

15 DR. WEISS: Post-market.

16 DR. SUGAR: That's assuming that we're  
17 going to approve the product now, which I presume, and  
18 that we shouldn't --

19 DR. ROSENTHAL: No. We can't presume what  
20 we're going to do, because we haven't voted it for it  
21 yet.

22 DR. SUGAR: No, but I can tell you what I

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1 presume. And my presumption is that we will approve  
2 it, and that we should not hold up approval of the  
3 product based on acquisition of this data.

4 DR. WEISS: Dr. McCulley, and then Dr.  
5 Macsai.

6 DR. McCULLEY: I would agree with Joel,  
7 but to put it back more broadly for Ralph, I mean, if  
8 it's not approved, then we would request that -- or  
9 recommended for approvable, that they be followed  
10 annually. If we do recommend approvable, which I too  
11 would - not being a voting - not going to get to vote,  
12 but I would. And I would be comfortable with that,  
13 and I would say then, I would prefer this -- as I  
14 said, I'd be comfortable with a recommendation for  
15 approvable with a post-market surveillance annually of  
16 that initial cohort. You had pre-ops for a total of  
17 five years.

18 DR. WEISS: Dr. Mathers.

19 DR. MATHERS: When you say "approval"  
20 there, you're talking about three different groups  
21 here, and they are very different. You have myopes  
22 for minus 3, myopes for 15 to 20.

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1 DR. WEISS: We're going to get to that in  
2 a moment.

3 DR. MATHERS: Okay. But that's -- I mean  
4 --

5 DR. WEISS: We're just talking about the  
6 specular microscopy portion, and then in terms of the  
7 different categories, we will be getting to that.  
8 Have no fear.

9 DR. MATHERS: Okay.

10 DR. WEISS: Dr. Macsai. And I'd sort of  
11 like to wrap-up this. Dr. Macsai, then Bandeen-Roche,  
12 and then I'd like to wrap-up this particular issue.  
13 Yes.

14 DR. MACSAI: I agree with Joel about  
15 post-market surveillance. I would add two comments.  
16 One, if approvable, it's got to be labeled that this  
17 stability has not been documented, and it's got to be  
18 an education for patients and physicians. And if data  
19 comes out later that shows there's massive problems,  
20 the FDA has an obligation to take an action.

21 Number two, if perhaps we're all wrong,  
22 and we don't have to wait until 2007, and at 2006 the

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1 biostatisticians, or 2005, the biostatisticians say  
2 hey, this was much ado about nothing, then the  
3 labeling be changed at that point, and we accept the  
4 statistician's interpretation that it is, in fact,  
5 stable.

6 DR. WEISS: With that in mind, if you want  
7 to put in labeling that stability of endothelial cell  
8 loss has not been documented, would you want to put a  
9 warning in there that there could be risk of corneal  
10 edema or no? Dr. McCulley.

11 DR. McCULLEY: I don't remember well  
12 enough. There are different implications to these  
13 words, and I don't --

14 DR. WEISS: Dr. Rosenthal. Would it be  
15 fair, if we're going to be putting in labeling that  
16 there is no documentation of a stabilization point as  
17 far as endothelial cell loss by specular microscopy,  
18 would it be fair to put in labeling there could be the  
19 risk, or the risk of corneal edema is undefined. Or  
20 because it's undefined, we shouldn't say it?

21 DR. ROSENTHAL: That's the panel's  
22 decision.

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1 DR. WEISS: Dr. Macsai.

2 DR. MACSAI: I don't -- we don't have  
3 corneal edema. We don't have one patient yet with  
4 corneal edema. What we have is --

5 DR. WEISS: Well, that's what we're  
6 talking about, isn't it?

7 DR. MACSAI: Right. But no --

8 DR. WEISS: That's what we're afraid of.

9 DR. MACSAI: No, what we're talking about  
10 is long-term endothelial cell loss. So what we say is  
11 that the data and the outcomes and long-term effects  
12 on the endothelium are unknown.

13 DR. WEISS: But for patient labeling, I  
14 think you'd have to put that in terms that it means  
15 something to someone, because endothelial cell loss  
16 doesn't have any significance to a patient. And I  
17 would maybe defer this one to Glenda Such.

18 MS. SUCH: Yes. I was just going to say,  
19 I don't know if this belongs in the labeling section  
20 of our discussion or not, but I was going to say there  
21 should be something at least at the bottom of the  
22 precautions that says something about the fact that no

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1 information is known about this beyond four years.  
2 Whether or not it's regarding this issue or any of the  
3 issues.

4 DR. WEISS: So maybe we'll get back to  
5 that when we get back to labeling. When we're talking  
6 about -- so we've talked about, and I think hopefully  
7 to your satisfaction, we've talked about a post-  
8 market study, and following the cohort. Does anyone  
9 want what's suggested, taking another fresh cohort of  
10 patients who are having this done after, if it gets  
11 approved, after approval, and following these  
12 patients. Does anyone want that?

13 DR. SCHEIN: May I make another comment?

14 DR. WEISS: Dr. Schein.

15 DR. SCHEIN: What is the logic of having  
16 a post-market surveillance study for an extended wear  
17 contact lens where not a single ulcer is seen in a  
18 pre-market trial? The logic is that there's a concern  
19 about the particular end-point, which requires a  
20 different kind of study. And I think the situation is  
21 exactly analogous. We have a new kind of device. We  
22 don't have any historical data to rely on. The

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1 situation is analogous to the way the rigid anterior  
2 chamber lenses were when ophthalmologists were putting  
3 them in their mothers, which is just after the  
4 pre-market approval. There was a lot of excitement,  
5 so I think to not set up some mechanism that's an  
6 early warning is completely irresponsible on our part.  
7 And I do believe it's the industry's responsibility,  
8 if they want to introduce these kinds of products.

9 The idea is not to stifle innovation. As  
10 you'll see, I'm going to be voting for approval. But  
11 the idea is to set up a mechanism that we can trust to  
12 either restrict labeling in the future, pull back the  
13 product, or to provide very sound information about  
14 its safety.

15 DR. WEISS: Well, in that case I think  
16 what we'll do is we'll confine that one to labeling.  
17 If anyone else wants to comment on specifically a  
18 labeling issue. Dr. Matoba.

19 DR. MATOBA: In the case of the contact  
20 lens issue, that we had an indication from your study  
21 that there was a certain risk for microbial keratitis,  
22 and here we don't have any information that there is

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1 that type of calamitous outcome that could occur, so  
2 here you'd be fishing.

3 DR. SCHEIN: The rate of retinal  
4 detachment is higher in this study is higher than  
5 ulcerative keratitis was in any of the other studies.  
6 The rate of cataract is higher, so it's not just  
7 corneal edema.

8 DR. WEISS: Dr. Bandeen-Roche, then Dr.  
9 McCulley, then Dr. Mathers, then Dr. Sugar. Not Dr.  
10 Sugar.

11 DR. BANDEEN-ROCHE: If you want to defer  
12 this to the safety discussion, that's fine. But I  
13 have to at least raise it now, which is that we saw no  
14 hint of stabilization through three years. I mean, it  
15 was just, you know, all of the year-to-year changes  
16 were pretty even. So suppose the data come in, and my  
17 overly pessimistic tendencies for once, you know, bear  
18 out, and we see exactly the same continuing rate of  
19 decline, once all of the data are in. Would you then  
20 declare the product safe and go ahead?

21 DR. WEISS: Dr. McCulley.

22 DR. McCULLEY: Yeah. Could we ask maybe

1 the FDA to respond to that? And could we also ask the  
2 FDA to respond to Oliver's suggestion for -- I don't  
3 ever recall a discussion at a panel, at least that  
4 I've been at, where that kind of study post-market  
5 surveillance, or whatever the term would be for that  
6 particular one, would come up. I'd like to hear what  
7 the FDA says about both of those issues in terms of  
8 authority and practicality.

9 DR. ROSENTHAL: We have a member of the  
10 staff from the Office of Science and Biometrics who's  
11 ready to address this issue for you. Dr. Roselie  
12 Bright.

13 DR. BRIGHT: One minute.

14 DR. ROSENTHAL: I still -- while Dr.  
15 Bright is getting ready, you still have to decide  
16 whether you want this fourth and five year data on the  
17 existing cohort before it goes to market, so you have  
18 assurance of -- a reasonable assurance of safety and  
19 efficacy. Or do you have that reasonable assurance of  
20 safety and efficacy now, and the follow-up can occur  
21 after it is put on the market. That is different than  
22 this type of approach, which is in addition to the

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1 follow-up of the endothelial cell.

2 DR. WEISS: So I think what Dr. Rosenthal  
3 is pointing out is we've put the cart before the  
4 horse.

5 DR. ROSENTHAL: A little bit.

6 DR. WEISS: And that if everyone is in  
7 agreement that we have no evidence there's  
8 stabilization of endothelial cell loss, then is anyone  
9 in the panel bothered by the potential of a continued  
10 cell loss rate of 2 percent per year in these  
11 patients. And if anyone in the panel is bothered by  
12 that fact, how do you justify that, or explain that,  
13 or accept that?

14 DR. McCULLEY: Jayne, I've said it before  
15 and I'll say it again. We don't have the solid data.  
16 We need more data. My sense of this, based on  
17 everything including my broad clinical experience and  
18 past history with things, is that I would be  
19 comfortable enough with this being recommended for  
20 approvable. But to further give us assurance and  
21 comfort that we follow it post-market.

22 DR. WEISS: Then I would ask you, Dr.

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1 McCulley, can you explain to the panel why you're  
2 comfortable with approval? What factors about this  
3 PMA in the face of no documentation of stabilization  
4 of the cell loss make you comfortable with approving  
5 this?

6 DR. McCULLEY: Okay. I don't think  
7 there's no documentation. I think there's suggestion  
8 that there is, but I don't think there's proof. And  
9 the suggestion to me is that we have stabilization in  
10 the cell size, variability in shape, and that it does  
11 appear that with a limited number of patients that the  
12 cell loss between years three and four is leveling  
13 off. And I've seen -- and in the absence of any  
14 apparent known reason for continued endothelial cell  
15 loss, absence of any known mechanism to support  
16 continued endothelial cell loss, those give me the  
17 degree of comfort that I think this is reasonable.  
18 But do I think I have data that would let me nail that  
19 down if I wanted to switch sides and argue it the  
20 other way? No. But I think that it would be  
21 reasonable to try to gather more data to give more  
22 comfort to everyone else, and to myself. I could be

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1 wrong. I don't think I am, but I have reasonable  
2 comfort, but I don't have as solid a data -- if I did,  
3 we wouldn't be having this discussion.

4 DR. WEISS: But the question for the panel  
5 really now is whether there should be pre-market data  
6 or post-market data, if there's --

7 DR. McCULLEY: And what I'm saying is, I  
8 think we have sufficient assurance now to recommend  
9 approvable with continued surveillance post-market.

10 DR. WEISS: Dr. Mathers, and then Dr.  
11 Macsai, and then Dr. McMahon.

12 DR. MATHERS: well, finish this  
13 discussion. That goes more to Oliver's question.

14 DR. ROSENTHAL: Finish your discussion  
15 about this.

16 DR. WEISS: Finish our discussion, and  
17 then go forward.

18 DR. ROSENTHAL: And then we'll move on.

19 DR. MATHERS: It's a philosophic point.  
20 You're saying that we don't know, so let's go ahead.  
21 I would say we don't know, so let's make sure before  
22 we go ahead. And again I'll say that I don't think

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1 that what we say about minus 10 to 15, or 15 to 20  
2 applies to what we say about the 3 to 10. But in the  
3 absence of some indication of safety in this regard,  
4 I think going ahead is not the correct answer.

5 DR. WEISS: Dr. Macsai.

6 DR. MACSAI: If you look at my review, I  
7 didn't make a slide of this - I'm sorry. I did make  
8 a table of the rate of annual endothelial cell loss,  
9 assuming a pre-operative mean count of 2,657, which  
10 was the pre-operative mean endothelial cell count  
11 here. And if we take the average loss, I'm not going  
12 to argue with Mike or Bill Bourne, but if you take the  
13 average loss at .6 percent by natural attrition, that  
14 would mean you'd lose 15.9 cells per year.

15 In that August '02 panel meeting that Dr.  
16 Grimmett did his report on, he said 1.5 percent would  
17 be okay. And that's 39.8 cells per year. This PMA  
18 has 1.8 percent, which is 48 cells per year. And then  
19 the ANSI Standard is set at 2 percent, which would be  
20 53.1 cells per year, so this PMA lies right smack dab  
21 in the middle between the recommendations of the  
22 August '02 panel meeting, and the ANSI - which was 1.5

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1 percent, and the ANSI guidance document referred to,  
2 which was 2 percent. So at 1.8 percent, it ain't bad.  
3 I just don't know if it's going to be bad in the  
4 future, so I think looking at these patients to five  
5 years is prudent.

6 I guess my question to -- I have another  
7 question I just want to ask Dr. Schein, since I can't  
8 ask him private, is - what if you look at this cohort  
9 for five years, this endothelial cell counted cohort  
10 for five years to see about retinal detachments, and  
11 cataracts, and I forgot what else you said. Would  
12 that answer your question? No?

13 DR. WEISS: Dr. Schein.

14 DR. SCHEIN: The reason it wouldn't answer  
15 the question is, one, sample size; and two,  
16 representativeness, the latter being more important.  
17 So I would want some sample of patients that are  
18 actually getting the device post-market, and some  
19 sample of surgeons that are doing it.

20 DR. MACSAI: Oh, to see who performs the  
21 same?

22 DR. SCHEIN: Absolutely. And also a

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1 larger number, but not for cell counts. That's a  
2 different story. That's a longer term issue.

3 DR. WEISS: Dr. McMahon.

4 DR. McMAHON: This is to Ralph, and this  
5 is sort of a semantics question, because we're dealing  
6 with a situation with regard to endothelial cell loss,  
7 where we kind of don't know. And so the obligation of  
8 the panel of voting on safety and efficacy, one can be  
9 that we have to have reasonable assurances that the  
10 device is safe, versus reasonable assurance that it's  
11 not unsafe.

12 DR. WEISS: Well, the way it reads is  
13 "reasonable safety and efficacy".

14 DR. McMAHON: Yeah, but I want to know the  
15 spirit of that view, because it makes a difference on  
16 how I would vote.

17 DR. WEISS: Well, I'll call on our  
18 spiritual counselor, Dr. Rosenthal.

19 (Laughter.)

20 MS. THORNTON: Ralph, could you speak into  
21 the microphone, please. We want to get this one.

22 MR. ROSENTHAL: The reasonable assurance

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1 of safety and efficacy.

2 DR. WEISS: Okay. So with this in mind,  
3 since it seems -- from what I understood from the vote  
4 before, most of the panel members didn't feel the  
5 stabilization was -- the data showed stabilization.  
6 Do most of the panel, even with that fact, would most  
7 -- those panel members who would feel that there is  
8 still -- this is still reasonably safe to have a  
9 post-market study, and go ahead with approval under  
10 any means, or we're not talking about what type or  
11 whatever, in terms of labeling or other issues. What  
12 number -- if you could raise your hands.

13 DR. ROSENTHAL: Excuse me, Dr. Weiss.  
14 It's a post-market follow-up of the existing IDE  
15 subjects.

16 DR. WEISS: Fine.

17 DR. ROSENTHAL: That's very different than  
18 a post-market study of another group of patients.

19 DR. WEISS: So we're talking post-market  
20 study in order to get further data, and approval with  
21 the information we have at the present. At the  
22 present point, and we haven't gone through the other

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1 issues, the members of the panel who would -- yes.

2 DR. BRIGHT: Well, I have a presentation  
3 that goes over what's appropriate for pre-market,  
4 what's appropriate after the device is allowed on the  
5 market, what you can get in a pre-market setting  
6 versus condition of approval, versus post-market. And  
7 that might short-circuit some of the questions.

8 DR. WEISS: Okay.

9 DR. McCULLEY: Jayne, can I say one thing,  
10 and I do want to hear what she has to say.

11 DR. WEISS: Yes.

12 DR. McCULLEY: In response to Bill's  
13 philosophical question, the issue is do we have  
14 reasonable assurance of safety and efficacy. I think  
15 we do. I don't think we have absolute, and I would  
16 like to go ahead and get the absolute. That's the  
17 reason for requesting additional surveillance. I  
18 think we have reasonable, but it's not absolute.

19 DR. WEISS: Would I be able to -- just in  
20 the interest of time, would you be able to show  
21 whatever that you have that speaks specifically to the  
22 choice of studies the panel might have, as opposed to

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1 the background information that you might have, that  
2 we could look at concrete stuff as far as what our  
3 choice in terms of studies that we might recommend?

4 DR. BRIGHT: Well, I have two concrete  
5 choices, but I want to lead up why I got there, if  
6 that's okay.

7 DR. WEISS: If you can make a quick  
8 lead-up.

9 DR. BRIGHT: I'm covering many slopes.  
10 Okay. Well, the disclaimer is that just because I'm  
11 presenting about those market studies, doesn't mean  
12 that I think it's approvable right now, but it would  
13 apply even if there was a later discussion about  
14 approvability.

15 The reasons for doing post-market  
16 assurance would be that the study population for the  
17 pivotal study is small, and not large enough to detect  
18 the potentially serious adverse events. And the study  
19 population for the pivotal study is highly selected.  
20 It doesn't include vulnerable sub-populations.

21 The study duration is typically shorter in  
22 real-world exposure, so we've been talking about the

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1 3 and 4 year effects, versus 30 and 40 years. And it  
2 can detect problems due to improper or unskilled use  
3 of the device in the real-world. And study centers --  
4 but the study centers that you already have the data  
5 from are typically highly skilled and motivated.

6 And another general reason is to detect  
7 adverse events due to drug-device, or device-device  
8 interactions that would not be detected in controlled  
9 studies. So questions that might need to be addressed  
10 for this particular device are the longer term decline  
11 in endothelial cell count, long term development of  
12 cataract. Dr. Schein mentioned some other outcomes.

13 Some issues for phakic IOLs is the prior  
14 history in the 1980s with an implantable lens that was  
15 associated with safety concerns after 10 years of use,  
16 so we would want -- might want an earlier warning  
17 system. And PIOLs could be implanted in a large  
18 number of young adults with moderate vision problems.  
19 And, therefore, in the worst case scenario, there's a  
20 potential for a large number of middle aged to elderly  
21 adults needing corneal transplants.

22 So what are the three authorities we have

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1 for requiring studies? We have the pre-market  
2 authority, the study has to be done in order for the  
3 device to get to market. But the disadvantage is a  
4 small sample size and short follow-up time. The  
5 condition of approval study is one where the approval  
6 is conditional until the results of that study are  
7 satisfactory, but you have to order it before the  
8 device even gets the conditional approval. And the  
9 post-market surveillance study, we can order that  
10 study any time, but patient and physician approval is  
11 the most difficult during that time because the device  
12 is freely available.

13 So in considering the type of conditional  
14 approval study, it has to be least burdensome. We can  
15 consider any appropriate study design, and it does not  
16 need to be simply an extension of the pre-market  
17 study. The sponsor could be asked to report progress  
18 and results to the panel each year if the panel  
19 desires, and the sponsor can use the results to change  
20 the labeling and marketing.

21 So there are two main types of  
22 observational study designs. There's case control and

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1 follow-up. The advantage of the case control study is  
2 you can be more efficient with a smaller sample size,  
3 but in this instance, I think it's impractical because  
4 I think the use of this device is likely to be  
5 relatively uncommon. And you also have to decide in  
6 advance what outcomes you're going to look for.

7 But in the follow-up study, you can enroll  
8 patients as they get the PIOL, so if it's vastly  
9 popular, you get your cohort up and running very  
10 quickly. If it takes longer, then it takes longer to  
11 accrue, but that's fine because it's affecting a  
12 smaller portion of the population anyway. You get  
13 flexible follow-up time, and you can discover new  
14 outcomes that weren't anticipated. But the  
15 disadvantage is are that you need to minimize the  
16 drop-out rate, and you need a large number of  
17 patients.

18 We worked out two options. There's  
19 nothing required about any of these, but they're  
20 basically discussion and talking points. The first  
21 option was called registry, so you could ask patients  
22 at less than one year intervals whether they had an

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1 ophthalmic visit for a problem. And we said less than  
2 a year because if we use the mail system, which is  
3 considered least burdensome of different kinds of ways  
4 you could contact patients, they're forwarding  
5 interval is one year. And you could ask a very simple  
6 question, did you have to go to the ophthalmologist.  
7 And then if they say yes, ask for the details for  
8 getting their records. And you could follow as many  
9 patients as possible for a decade or more, whatever  
10 time period the panel is interested in.

11 The advantages are, you can readily  
12 describe and identify the population of users in the  
13 event that some kind of regulatory intervention is  
14 needed. And it's a relatively inexpensive study. The  
15 disadvantage is that there's no early warning of  
16 impending problems. You get the warning when somebody  
17 has the problem that's bad enough to go to the  
18 ophthalmologist.

19 The other option that could be considered  
20 is something called a nested cohort, where you could  
21 build on the existing clinical trial population, and  
22 then sample some new patients, collect cell counts at

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