DR. HILMANTEL: Yeah. That's true that it can vary from visit to visit. You may have some patients pop up above whatever level you choose, but equally you can have patients, if it's just random, you'll have patients dropping below that to kind of balance it out. So I think it's a reasonable approach to look at the proportion that were below whatever number you want to look at. But you do have to recognize that there are limitations to that and be aware of it.

DR. WEISS: Dr. Bandeen-Roche.

DR. FERRIS: Can I just follow up on that question?

DR. WEISS: Are you going to continue that question or is it --

DR. BANDEEN-ROCHE: Yes. And I might dovetail to you actually as well because I do strongly agree with Dr. Ferris' comment and, you know, listening to Dr. Musch, I wonder whether something like a quantile regression would be useful here. I understand it's not straightforward, you know, for the same reason that the exponential model isn't straightforward, you know, but it seems to me that that might get at the question of, you know, risk of being below a certain amount while taking

some smoothing into account.

DR. HILMANTEL: We did struggle with this data. We looked at it in several ways. One way that it was looked at was the sponsor used their biexponential model and then used the distribution of the residual measurements around the regression line at postop time points. They used that to project the proportion of eyes that would be below certain, say 1,000 at different time points, or 750 at different time points, and that's presented in the executive summary. If you look at the projection at 48 months for those tables, it's very close to the numbers that I presented as observed at the final time point.

DR. WEISS: Dr. Ferris.

DR. FERRIS: Just to follow up on that, I'll take off my epidemiology hat and put on my clinician hat, and that is, what about time to event where the event is corneal edema, because we're looking at this surrogate, and then we've got a model of the surrogate, and at the end of the day, what we'd like to know is what's your risk of developing corneal edema over time?

DR. HILMANTEL: We didn't do that. I mean we couldn't do that.

DR. WEISS: Dr. Szlyk.

DR. SZLYK: Just a quick question. Do you have any data available on or did you dissect the data by acuity levels and ECD levels just to get an idea of the risk in that better acuity group from 20/80 to 20/160?

DR. HILMANTEL: No, we didn't do that, and you do have to recognize that, I mean this is a study of approximately 200 people enrolled, and you have very noisy data, and the more you slice and dice it, the more difficult it gets to get a precise estimate of something. You can estimate whatever you want, but the confidence limits on that would be quite wide.

DR. WEISS: With that in mind, the final preferred group of 33 that had the deeper AC and the better characteristics, what would be the noise to be looking at that particular group to say that's who should be getting this implant?

DR. HILMANTEL: Well, I mean I presented that in my slide. The group of 33, the main restriction, the main additional restriction in that group was the cornea specialist requirement and, you know, there was only --

DR. WEISS: No guttata.

DR. HILMANTEL: -- a limited number of

cornea specialists in the study, and a lot of them lost eyes in the LTM phase of the study. So as I mentioned, if you look at the cornea specialists, in the LTM phase, most of those eyes came from one or two sites. I believe Dr. Stulting's site was actually one that contributed the most in the LTM phase in that restricted group.

DR. WEISS: Does anyone have any other questions for -- I guess I just want to clarify that. So is that yes, there's a lot of noise? Or yes, you could say it would have statistical significance?

DR. HILMANTEL: Well, if you look at the slides that I had, and I can put them up again, but there's a very wide confidence interval on these rates for such a small group. So the level of surety of safety that you have, if you're only basing it on a small group like that, is very limited.

DR. WEISS: Okay. Are there any other questions from the Panel?

(No response.)

DR. WEISS: Can we now get sponsor's comment on that one slide before we go to lunch?

DR. EYDELMAN: I was told yes.

DR. WEISS: There was a percentage of patients who lost vision, the slide that added up to

100 percent. If you have a comment, you're welcome to make it now, and if you do not, we will break for lunch. So whatever you prefer, Mr. Hill.

MR. HILL: Madam Chairman, I'd recommend we break for lunch so we can pull up that original table. I know the answer, but I want to show you the --

DR. WEISS: I see a hungry sponsor. That's what I see.

(Laughter.)

DR. WEISS: So we will now break for lunch. We will reconvene again in this room 45 minutes from now, and I mean 45 minutes. Please take any personal belongings you may want with you at this time. The ballroom will be secured by FDA staff during lunch break, and you won't be allowed back in the room. So if you want it, take it with you.

I have 1:00 p.m. 1:45 we'll start again.

(Whereupon, at 1:00 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:45 p.m.)

DR. WEISS: So we now reconvening the second half of the meeting, and we're going to proceed over the next hour and 15 minutes with Panel deliberations addressing the FDA questions. There are seven of these questions.

Now during the session, this is mainly for Panel discussion. However, we will at various points being asking the sponsor if there's a question that we want to clarify, give the sponsor the opportunity to give us the clarification during this portion.

Dr. Eydelman, I have a question. Would you want us to take this opportunity to have the sponsor address those couple of outstanding issues or have them addressed as the questions that pertain come up?

DR. EYDELMAN: This is at your discretion fully.

DR. WEISS: Does the sponsor have some answers to some of the questions that were asked previously that they would like to come up to the podium for?

MR. HILL: Yes.

DR. WEISS: That's fine. And I would also request if you could sort of give the answers as

briefly as possible, as succinctly but correctly. So thank you.

(Laughter.)

MR. HILL: Will a yes and a no suffice? There was a question regarding the stratification of the visual acuity and the outcomes. I'm paraphrasing this somewhat. On individuals who had preoperative visual acuities in the moderate group, 20/80 to 20/160, 87 percent of these subjects gained 2 lines of distance or near vision, 47 gained 2 lines of distance and near vision, and 13 percent gained 3 lines of distance and near vision, 53 percent gained greater than 2 lines of distance visual acuity, and 13 percent gained greater than 3 lines of distance only vision. Baseline visual acuity, Chet, do you have that on that group? I believe Dr. Musch asked that question.

DR. EDRINGTON: Was there any loss?

MR. HILL: We're attempting to find that right now. We have not been able to do it. Whatever it may be, it must be very minor because there were only 14 patients in this cohort. The --

DR. GORDON: Allen, one.

MR. HILL: Pardon me.

DR. GORDON: One.

MR. HILL: One. I have an answer. One.
DR. EDRINGTON: One.
MR. HILL: Okay. I'm out of date. In terms of the baseline visual acuities are depicted here. So you can see them. In terms of the moderate, severe, and profound visual acuity.
DR. WEISS: So that answered the question for the Panel. Everyone's satisfied? Okay.
DR. EDRINGTON: Can I ask a follow-up?
DR. WEISS: Yes, Dr. Edrington.
DR. EDRINGTON: On the one that last some visual acuity, was there an explanation for that?
MR. HILL: I do not know. I don't have the -- I don't know. I'll see what I can find here.
DR. WEISS: Okay. Were there any other questions that you had wanted to address?
MR. HILL: I'm looking for Janet Wittes.
MS. WITTES: I'm here.
MR. HILL: Oh, there she is. Yes. We had a question from Dr. Bandeen-Roche that we're going to answer.
DR. WITTES: A couple of questions for you. Here's a question about the 22 pairs of eyes. The mean visual acuity for the IMT was 20/300 and for the fellows, 20/200. And, of course, the eye that was

worse is the one that's in the group.

Okay. Next, next, next. All right.

DR. WEISS: I have a question on that slide. Was that a preoperative or this was one of the --

DR. WITTES: Preop.

DR. WEISS: Have they had an IOL at any point in time prior to --

UNIDENTIFIED SPEAKER: No.

DR. GORDON: What Janet is presenting is the 22 eyes that underwent cataract extraction and IOL implantation during the study. So they may have a baseline pre-IOL and the postoperative post-IOL.

DR. WEISS: And actually a quick follow-up question on that. Was the nucleus gracilis similar? Did anyone look at -- because even they're two eyes of the same patient, we don't know if the cataracts were the same. So was there any control to see if the cataracts were fairly similar preop or we don't know that.

DR. GORDON: We should be able to find that information for you.

DR. WEISS: Thank you.

DR. WITTES: Okay. Question about survival analysis. It wasn't performed on a lot of these

variables partly for the reason that Dave had mentioned, that things go back and forth. This analysis just done, the last postop visit. So the IMT-implanted subjects, 10 of them, 5 percent in the IMT eyes and 14 percent had loss of more than 2 lines, but the time to events analyses were not done, and most of them can't really be done.

Okay. This is an analysis just hot of the press. So if you ask any more questions about it, I'll say I don't know.

Is that okay, Karen? Can we move on?

DR. BANDEEN-ROCHE: Okay.

MS. WITTES: Okay. Next. Okay. The question about the biexponential model, here's the observed and fitted means. So they're very close. It's a four parameter model. It's not surprising that it's a very good fit. The question that you asked about, the within subject correlation, we obviously struggled with this. The models that we tried failed to converge, and so one of the ways of looking at it, so what's the 6 percent? In a formal way, the 6 percent is you take the four parameter model, you fit the confidence in, you get the 90 percent. You get a 6 percent. But you can look at it as just 6 percent is twice the observed, and so

even if the observed loss per year is 3 percent, 6 percent is twice that which is bigger enhanced conservative but the model, but in answer to your narrow question about did this include the within patient correlation, no.

DR. MUSCH: Dr. Wittes, the fact that the -- I think the piecewise linear mixed regression that the FDA did probably fit because they modeled the period of rapid decline and then modeled the period of rather linear loss, wouldn't you say? I mean if you try to fit a linear mixed regression to a pattern like that, it won't converge probably.

DR. WITTES: Well, I mean I think your idea of quantile response is --

DR. MUSCH: Yeah.

DR. WITTES: -- but I think the way to think about it is sort of non-statistically, just is 6 percent consistent with the data seen, and it's actually twice the observed.

DR. MUSCH: Twice.

DR. WITTES: Okay.

DR. WEISS: Okay. One, if the sponsor is set, we have one question here.

DR. SUNNESS: I was just wondering about the question, if you just look at the group that you

have the long-term study on as well, if you get the same rates for endothelial cell loss?

MR. HILL: The answer is, while not presented today, the answer is yes.

DR. WEISS: Okay. So that was -- I'll just identify that was Dr. Sunness and Mr. Hill, and so now if we're set with the questions that were floating, we're going to onto the FDA IMT Panel meeting questions, and that will guide the discussion, and if the FDA can perhaps project those.

The first question: The sponsor has presented specular microscopy data from IMT-002 and IMT-002-LTM. Morphometric analyses were collected under both protocols. Considering the surgery-related decline in ECD, the chronic rate of ECD loss, the morphometic analyses, the proportion of eyes that declined to low ECD levels, and the number of cases of decompensation and late corneal edema, please address the following -- and we'll address these one by one.

A, which is the first thing we're going to address, please discuss whether the ECD and morphometric data provide reasonable assurance that the long-term risk of corneal decompensation will be acceptable, acceptable is the word we're looking at,

for the intended population?

So I'd like to throw this out to the Panel and whoever, you know, would like to start the discussion. Is the long-term risk of corneal decompensation in the studies presented acceptable for the intended population? Dr. Ferris.

DR. FERRIS: Thank you so much.

DR. WEISS: Oh, I know.

(Laughter.)

DR. FERRIS: So what's acceptable? And, you know, people take all sorts of treatments that are very high risk because they have an interest in the benefit. And as I said earlier, I think what I would need if I was trying to decide whether I wanted this implant, and I might well want this implant if I had geographic atrophy, is some reasonable estimate and I would say not -- a conservative estimate in the sense of 6 is a doubling of 3, what are the proportion of eyes that are at risk. If I look at the skewed distribution, there are 20 percent of those eyes that look to me like they're at risk for corneal edema, and I'd like to actually -- and I'd still like to know what is the rate of corneal edema in this subgroup. And I would present that information to the patients. Here's the benefits,

here's the risks, and you decide.

DR. WEISS: So, to you, that if a percentage could be given, whether it's 5 percent or 25 percent, if you could quantitate a percentage to put in an informed consent, then that could be acceptable.

DR. FERRIS: To me it is, and the unfortunate thing to me is that we have data maybe going out to five years, and I understand because I talk to these patients all the time, that when you say, you know, your 5-year risk or 10-year risk, oh, honey, I'm not going to live that long. Well, the reality is they are going to live that long, or at least 50 percent of them are going to live 10 years. So I think the nagging concern is that there is this potential time bomb of some proportion of the patients who are going to develop corneal edema and need something more, and if they know it up front, I don't think it's a problem. If they think everything is just fine, that's where I think there's a problem.

DR. WEISS: So I would ask you as a follow-up, is there an upper number that you would say, even if a patient was informed, it would not be acceptable?

DR. FERRIS: So I looked at the Stargardt

stuff and I was pleased to hear the sponsor say, you know, 50 percent is just beyond what we think is reasonable, and I was wondering what would be reasonable to me, and if it was 10 percent risk or 20 percent risk, as a 10-year risk, and it made a difference between whether I could get around or not, I think that's a legitimate risk. My problem is I don't -- it would be nice if I could give some better estimate to my patients as to what that risk is.

DR. WEISS: So in your mind, if you could quantitate it, that would be the first requirement, and if you could quantitate it in your mind, 20 percent or less at 10 years would be reasonable or acceptable?

DR. FERRIS: Yeah, and I think that's where this data is. I mean it's around 5 percent or so at 5 years or 3 percent. I have a hard time figuring out what the denominator is here for the corneal edema issue, but I think they could come up with some estimate, and to me, that's the key for this device is to give the patients some fair warning and also some fair estimate of what their benefit's going to be.

DR. WEISS: And that's why actually as members of the Panel comment on this question, I've

taken the Chair's prerogative to ask you individually what your upper limit would be because if data can subsequently be calculated another way to come up with a number, it might be helpful for FDA or whatever to be guided by what the upper limit might be. Dr. Matoba, then Dr. Bandeen-Roche.

DR. MATOBA: Okay. So I agree with Dr. Ferris but, too, the comments about the endothelial cell loss risk, we should also make sure that the patient is informed that -- well, if you look at the number of lenses that were not implanted intraoperatively and then the number that were taken out postoperatively throughout for the various reasons, there's about a 9 to 10 percent chance that they won't be able to have the lens at all, and then that subset of patients may have a sight risk or other types of types of complications. So that should be added to whatever endothelial cell problems they may have.

DR. WEISS: And this doesn't totally address this question, but it would address labeling. Perhaps we could -- you could scribe that --

DR. MATOBA: Yeah, true.

DR. WEISS: -- is that if other -- if you develop a corneal complication, you should be aware

that other complications could be associated.

DR. MATOBA: Yeah. It goes to Dr. Ferris' point that of he would like to divulge or have a simple way to inform the patient of the actual risk of attempting the implant.

DR. FERRIS: I'd be interested in what the FDA people think with regard to the predictability of low endothelial cell count based on starting endothelial cell count. This is in my data, but I'm just looking at it, and it doesn't look like it was that good of a predictor as to who was going to wind up in the lower quantile.

DR. WEISS: I think that's going to speak to the question of the grids that we're going to get to in a bit. So I'm going to hold off on that. Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: So I would say that I agree with the spirit of the comments that have come so far. It's important to characterize the risk in terms of not only the mean but in terms of the percentage of patients who can expect to have an adverse outcome. Just to comment on the numbers that are being thrown out, someone please correct me if I'm wrong, but I think we're at about 15 percent seems to be the overall, not the guttata free I don't

think, estimate at 48 months of an ECD below 1,000 is it? You know, so I don't know what the cutoff we're using is, and then you just mentioned the percentage who can expect to not even be successful with the implant.

DR. WEISS: And be out of the study by then.

DR. BANDEEN-ROCHE: And be out of the study by then and, you know, so those numbers are already up there.

DR. WEISS: So I would question that, and perhaps the data that we have is as good as we can get, and I don't know, but let's say in the situation that this magic number cannot be achieved by anyone in this room and what you see is what it is, and if the number's let's say 15 percent at 2 years or was it 4 years.

DR. BANDEEN-ROCHE: Four years.

DR. WEISS: At four years below 1,000, if that's what we've got, is that acceptable?

DR. FERRIS: But I'd like to be clear that I view that number as a surrogate, a pretty noisy surrogate, and that's not what I was talking about.

DR. WEISS: I totally understand. I know it's not what anyone here wants, but what I'd like to

do is perhaps help FDA in that we all want a lot of things in life and most of it don't happen. So if this falls in that category and all we have is what we have and what we have is 15 percent ECD below 1,000 at 48 months, that's what we're all looking at, at this moment, is that acceptable?

Let's go around the room. Just -- Barbara, if we could start with you. Is that acceptable?

MS. NIKSCH: My answer would be yes.

DR. WEISS: And you can abstain also, but you can yea, nay or abstention. Mr. Bunner.

MR. BUNNER: I would think so, and just from my perspective being not nearly as technically --

DR. WEISS: Well, that's what we want, your perspective. That's why you're here.

MR. BUNNER: -- is we're also talking about individuals facing a severe visual impairment to begin with, and I think for the consumer, that risk equation is different than other risk equations we face in life. So I think I would be more acceptable, although a greater risk factor, in making that option than I would be under other circumstances in healthcare. So, yes.

DR. WEISS: Dr. Ferris.

DR. FERRIS: I actually agree.

DR. WEISS: So what we have, you would say, would be an acceptable risk level if the patient was adequately informed?

DR. FERRIS: Right. And I would add that what's acceptable for the Hamlet types is going to be different than Admiral Ferris. I mean there are going to be people who look at this very differently, and so I think you need to give them the numbers and let them choose it. It's not up to me to choose.

DR. WEISS: Dr. Szlyk.

DR. SZLYK: Yes, I agree it is acceptable; however, I would want to characterize the risk by something that could be easily understood by the patient, by visual acuity levels and by age.

DR. WEISS: So I'm heading into another questions, so I really don't want to head totally into another question, but if, and I think we would have to address this, that it would be incredibly important in terms of deciding how that patient would receive that information and, too, you can't guarantee the patient would receive the information, but as close as possible to a guarantee I think would probably be partnered with accepting that risk for some people. Dr. Matoba.

DR. MATOBA: Yes.

DR. WEISS: Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: So my gestalt is yes, I definitely defer to my visually, you know, specific colleagues for their expertise on this.

DR. WEISS: I guess I'll give my opinion last. Dr. Sunness.

DR. SUNNESS: Janet Sunness. I guess I also think it's probably acceptable, but I do agree with the ECD loss is not what we're looking for, really looking for, how intact the cornea is and whether they should be given, you know, a percentage, the risk of corneal transplant is this and this.

DR. WEISS: So this all speaks to labeling and informed consent and perhaps physician labeling, patient labeling, informed consent, perhaps even the course that's given to the physicians or the visual training, perhaps any or all of these aspects as far as what information is imparted to the patient as far as trying to quantitate the risk associated with the cornea. Dr. Edrington.

DR. EDRINGTON: Yes, with proper patient education.

DR. WEISS: Dr. Higginbotham.

DR. HIGGINBOTHAM: Agreed.

UNIDENTIFIED SPEAKER: Yes.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: As the Panel continues their deliberation, I would like to ask that you specify which parameters or which -- what it is that you would like to see, and just to reiterate what you've said before, we have a lot of data sliced many different ways. So if it is that you're asking for some additional data or additional analysis versus just supplying the data that was performed in a different manner, please be clear in your recommendations.

DR. WEISS: So one thing that has been asked for, is there a way to tell a patient at four years time, if you enter the study at time zero, at four years time, your risk of having frank corneal edema will be XYZ. Your risk of having undergone corneal transplantation will be XYZ. It sounds like that's the number that people want. Is that number possible to achieve through any other statistical manipulations?

DR. EYDELMAN: I'm going to ask Dr. Hilmantel to comment.

DR. WEISS: Gene.

DR. HILMANTEL: I mean, yeah, we can do a

survival analysis to give that type of information. There's some question about whether the people who continued on in the study actually had some bias. So the results may be questionable.

DR. WEISS: Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: I was going to get back and try to address the overall characterization of the risk, and so that is absolutely one concern is the extent to which the later cohort is biased or comparable to the former cohort, not just on demographic measures but in terms of their rate of ECD loss, leading up -- I mean, you know, so whatever can be brought to bear in terms of things that are directly relevant to their subsequent risk. And then since I guess I have the microphone, I'll also comment that, you know, in terms of the long-term risk being characterized, absolutely not in my point of view, meaning the years of characterization, you know, that is sort of embedded within the grid, and I think that my recommendation would be to make very explicit to patients that, you know, our ability to characterize the risk beyond four or five years is severely limited.

DR. WEISS: Do -- yes, the sponsor has a comment. Mr. Hill.

MR. HILL: Thank you. Allen Hill. Just a couple of comments regarding Dr. Ferris' in terms of projections and what the actual numbers are. We've had 90 individuals that have late onset corneal edema unresolved, out of that which is 4.4 percent of the implanted population. Two percent, or four out of that population have had cornea transplant. In terms of prediction, just in terms of the actual number right now at, I'll use the 750 number, I don't have the 1,000 right on the top of my head, but at 2 years, that was 24 months which we have almost all the population. That number was 7 percent of the population, and it's slightly higher for the population that we have available to us at 48 months, and then if we utilize the predictive model, at 48 months, the predictive model predicted 7 percent which is very, very close to the actual number.

If I were to go back in time and use that predictive model to predict out to 48 months, which we've done, we used 24 months to predict 48, the accuracy was quite good.

So we agree. We can provide that, you know. It is predictive, and we have all the issues with these predictive models.

DR. WEISS: And I would just ask FDA

statistics to comment on whether they would agree with that number at the end of the game.

MR. HILL: One more comment.

DR. WEISS: Yes.

MR. HILL: Just the LTM comparability, I know I mentioned this earlier. They're very, very similar populations. There's not much difference in them at all but --

DR. BANDEEN-ROCHE: The demographics, right?

MR. HILL: Yes, absolutely.

DR. WEISS: I guess I said I would reserve my comment to the end, and I think the thing that's coming across is certainly there's a higher risk, and certainly there may be an increasingly higher risk because the numbers or the spread is very large and there are people falling below the line. And then the question in the best circumstance, it doesn't happen, and in the worst circumstance, there's an epidemic. So if you're trying to guard against the worst circumstance, how do you inform the patient and what do you inform the patient with so they are informed that they could fall into that possibility because I don't know if we can get a number. But does FDA agree with those numbers presented?

DR. HILMANTEL: Yeah, I'm Gene Hilmantel. The numbers that the sponsor provided are the numbers that were projected from the biexponential modeling based upon the distribution of residuals around the regression -- Again, there's a lot of assumptions in that.

DR. WEISS: What's the FDA's worst case scenario? Let's say there are a lot of assumptions around the biexponential model. So if we gave a worse case scenario, from using a different modeling system at 24 months, instead of 7 percent, what would you estimate it would be? Is there any data?

DR. HILMANTEL: Well, the worse case, I mean we presented in our slide. We presented confidence intervals about the rate of edema and the rate of being below certain levels of cell counts. So we can pull up that slide if you want to see that but --

DR. WEISS: A number. The people here are just talking, we want a number.

DR. EYDELMAN: Well, perhaps you can pull up those slides then.

DR. WEISS: Now while we're pulling up the slide, I think we sort of have the answer to part 2 of question 1. Please discuss whether specular

microscopy data provides sufficient characterization of long-term ECD results. Does the Panel feel that specular microscopy data provides sufficient characterization of long-term ECD trends?

Dr. Matoba.

DR. MATOBA: It has its limitations, but I mean there aren't that many other things you can follow, but may I make a comment about --

DR. WEISS: Yes.

DR. MATOBA: -- all this talk about cell loss. I mean I think there's some patients who would want the implant enough that if you told them there's 100 percent chance you'll need a corneal transplant in 5 years, they would still say I want it. I mean as a cornea surgeon, doing the transplant is not the worst thing in the world, you know. It's not --

DR. WEISS: So you're saying again, informing the patient --

DR. MATOBA: Right.

DR. WEISS: -- as best as possible of the numbers, and if we don't have the numbers, just informing them that there is an increased risk we think, but we can't quantitate what it is.

Dr. Ferris, I don't think my last wording was good. So you don't have to comment on it because I would

disagree with it myself having said it.

(Laughter.)

DR. WEISS: Yes. Do we have -- yes.

DR. HILMANTEL: Yes, this is the slide that shows sort of the raw risk I guess you would say of getting below 750 cells per square millimeter, and if you look at the 95 confidence interval in red, there is the upper confidence limit for being below 750 is 14 percent. Here's the edema rates, unresolved edema. The upper limit for that estimate is 8.1 percent.

DR. EDRINGTON: Can you go back to that slide that has --

DR. HILMANTEL: This one.

DR. EDRINGTON: The one with the yellow background. It's times edema observed.

DR. HILMANTEL: This one?

DR. EDRINGTON: The sample size on the left is the 200 or so. The sample size are the ones that occurred on the right.

DR. HILMANTEL: Yes.

DR. EDRINGTON: That's a much smaller sample side.

DR. HILMANTEL: That's correct. You had 123 people in the implanted cohort continuing on into

the LTM phase of the study, and at any one visit, there was a maximum I think of 101 available patients at those visits.

DR. EDRINGTON: That's 5 percent just over that short period of time?

DR. HILMANTEL: 5 percent, I'm not sure what 5 percent you're talking about.

DR. EDRINGTON: Well, it's 5 incidences in 101 sample size, and that's over a short period of time?

DR. HILMANTEL: That's approximately correct.

DR. FERRIS: Well, there are 10 there, aren't there? And the life table is not so bad here because there's only one R with a question mark that I see. So in general it looks like if you did a life table on that --

DR. HILMANTEL: Yeah, we can do a life table.

DR. FERRIS: -- that that would give you some estimate of risk, and when I said that I had trouble with the denominators, if these things are happening over time --

DR. HILMANTEL: Yes.

DR. FERRIS: -- and a lot of them are out

at 40 months, where the denominator is not 217 --

DR. HILMANTEL: Right.

DR. FERRIS: -- the denominator --

DR. HILMANTEL: I understand what you're saying.

DR. WEISS: So you're saying that you would like a life table to help quantitate the risk for the patient?

DR. FERRIS: Just based -- those numbers look -- those are real events to me --

DR. BANDEEN-ROCHE: I'd like to second that.

DR. FERRIS: -- and give some estimate.

DR. BANDEEN-ROCHE: I mean, you know, some sort of a survival analysis that takes account of the --

DR. HILMANTEL: Yeah, I understand what you're saying. That makes sense. I just want you to understand the rate will be higher.

DR. FERRIS: Well, that's right.

DR. WEISS: So what I'm hearing the Panel say is there -- I'm hearing some sentiment that even if the rate was let's say 50 percent, you would not accept, but Alice, you would accept the 50 percent rate if the patient was informed and they accepted

the 50 percent rate.

DR. MATOBA: Well, I would say I don't think having a corneal transplant is such a terrible thing, and I guess if it were me and I had bilateral macular degeneration, I might take that risk to be able to see for five years. I mean I'm just saying that there will be some patients who will still want that. So I wouldn't necessarily say no, you can't have it because you might need a transplant in five years.

DR. WEISS: So to sort of summarize the answer to A and then before we go to B, and hopefully B will be fairly clear, is that this is acceptable if the risk can be better quantitated and the acceptability depends on the individual perception of the patient, whether or not they're risk adverse.

DR. EYDELMAN: Just to clarify. So the consensus is that there is no ceiling, in other words, no percentage beyond -- I'm trying to get as much information as possible to avoid having to come back to Panel.

DR. WEISS: No, I agree. I agree.

DR. HILMANTEL: If we calculate a rate based upon -- I'm sorry. I'm Gene Hilmantel. If we calculate a rate based upon the survival analysis and

we calculate a confidence interval on that, is there some upper limit that the Panel will find unacceptable?

DR. WEISS: Gene, will this be calculated at like 48 months or at what time point would this probably be?

DR. HILMANTEL: The survival analysis uses all of the data. You're estimating the time to an event. So here would be the time to an unresolved edema, and so you get an estimate of the time, and then with that you can estimate your chances of getting the --

DR. WEISS: Well, I would like to frame the question to the Panel members and go around. So I could frame it saying at 48 months, what would be your upper limit of risk, but is there a better way to phrase it that would apply to the type of statistical analysis you'll be doing? So if you'll help me with phrasing the question in terms of getting the upper limit.

DR. HILMANTEL: Well, we'd like to know if we come up with an estimate of the risk within 48 months.

DR. WEISS: Okay. Fine.

DR. HILMANTEL: Okay. Is there an upper

limit for the estimate of the risk, and is there an upper limit for the confidence limit on that?

DR. WEISS: So at 48 months, and a confidence limit is -- I wouldn't feel that secure actually giving you the confidence limits myself, but I would feel better about telling you what my perception of the risk would be, but going around 48 months, what's the upper limit at which point even if a patient accepted it, you would not want to offer it to them because -- just because someone wants it, it still may not be reasonable, and that's -- Dr. Musch, is there an upper limit of risk beyond which you would not want to even offer to a patient?

DR. MUSCH: We have to weigh benefits and risks as Rick mentioned early on. So I find it difficult to focus on one number.

DR. WEISS: 90 percent. If you said 90 percent, your cornea is going to get edematous, would that be acceptable in any circumstances?

DR. MUSCH: Surely that, and probably less than that because we don't want to be promoting, you know, the corneal transplant surgeons' practice in here --

DR. MATOBA: That's why I make those comments.

DR. MUSCH: -- but I'd probably, given what I see, I think and all I want to say, don't focus on upper limits of confidence intervals because that's driven by sample size.

DR. HILMANTEL: Especially out of 48 months.

DR. EYDELMAN: But unfortunately we have to deal with the data that we have.

DR. MUSCH: That's why I said don't hang your hat on an upper limit of a 95 percent confidence interval.

DR. HILMANTEL: This is Gene Hilmantel again. The upper confidence limit is actually something that's fairly important to us. A study can be done with 10 or 15 eyes and get a 0 percent rate, and it doesn't tell us much. What's important to us is the evidence that that sample size provides.

DR. MUSCH: Well, you will have robust information through 24 months and fairly, I don't know what the term is, non-robust information after that. So we can talk about 24-month rates and confidence intervals associated with it, but much beyond that, then look at your point estimates and don't get too swayed by where the confidence limits are.

DR. WEISS: Well, maybe what I'll do is this. I'm going to throw out some numbers and raise your hand if you think it's acceptable. 90 percent corneal edema at 48 months. Is that acceptable? So 90 percent not acceptable.

75 percent, is that acceptable? No one's going for 75 percent.

DR. FERRIS: Is it even reasonable? I mean we have data that shows that --

DR. WEISS: I think FDA -- well, just bear with me --

DR. FERRIS: Okay.

DR. WEISS: -- for three more numbers. 50 percent, reasonable?

DR. FERRIS: I don't think it's reasonable given the data that we have. It would be okay with me if it was --

DR. WEISS: If it's okay with you, then it's -- because we don't know what numbers are going to get crunched. So I'd like to -- I'm just trying to give FDA as much information as possible. So if there was a chance 50 -- half the people got corneal edema at 48 months down the line, how many of us would feel it would still be reasonable to implant giving the patient informed consent? Alice, come on,

raise that hand.

DR. FERRIS: It's at the edge.

DR. WEISS: Okay. So most of the Panel do not feel if it was a 50 percent becoming edematous at four years down the line, that would be acceptable. 30 percent, is that acceptable at 4 years down the line?

DR. HIGGINBOTHAM: Closer. Say 20 percent.

DR. WEISS: So 20 percent. Is that acceptable four years down the line? So what I find is what people are saying versus what they're voting on seem to be quite different: 20 percent is acceptable 4 years down the line; 50 percent is not acceptable 4 years down the line. Eve.

DR. HIGGINBOTHAM: Eve Higginbotham. We already said in the Stargardt subgroup that 50 percent in that group was unacceptable. So I can't, from that, extrapolate to the overall and say 50 percent is acceptable.

DR. WEISS: Okay.

DR. HIGGINBOTHAM: So it's somewhere between 0 and 50. And I don't know if we actually can really say. You're asking what we will accept. I mean given the burden of disease and my father, before he passed with age-related macular

degeneration, so I know how horrible an existence this is, so I agree with Alice that patients will agree based on, you know, the timeline of when they might anticipate that there may be an issue. If it's four years out, they will probably say yes even at 20 percent.

DR. FERRIS: The Stargardt is totally different, and it's different because it wasn't that they got a complication. It was because they didn't like the thing.

DR. WEISS: Right.

DR. FERRIS: And now you're putting in something where the benefit side. That's what David said earlier. You've got to be -- in each one of these, you have to balance the benefits and the risks, and they're different for AMD than Stargardt as I'm looking at it.

DR. WEISS: Okay. I'm going to have Dr. Eydelman comment, and I think basically we're not getting to the bottom line of this question. So I want to go on from here, and perhaps we can get at the answer another way, but what we are finding is basically the Panel feels that if a 20 percent risk is acceptable at 4 years, a 50 percent risk is not acceptable, and where it would fall in between is yet

to be decided.

I was going to go onto 1b unless you wanted to comment.

DR. EYDELMAN: I just wanted to draw your attention back to this slide. As Dr. Hilmantel pointed out, unfortunately the reality is we do need to look at the confidence interval because unless you ask for a new study, we're not going to be having any additional data. So we need to interpret the data with the inherent variability. So we didn't get to the point of the intended population, but should your discussion come back to the population, please keep in mind that this table summarizes the three different cohorts and the upper confidence that are currently calculated for these three cohorts. So it's 8.1, 6.3, and 20.2.

DR. WEISS: Dr. Bandeen-Roche, then Dr. Ferris, and if we can just have the comments very focused on this particular point before we go onto 1b.

DR. BANDEEN-ROCHE: So I do agree that the extent of variability of the estimate has to be accounted for somehow. It doesn't mean just do, you know, the most obvious seat of the pants analysis and just calculate whatever confidence interval. I'm not

saying you've done that. I know that sounds terrible. I'm not saying you've done that, but a careful analysis that tries to use the data to the fullest extent possible and then think hard about what is the, you know, degree of precision that's needed. You know, I think to totally ignore the precision, I would not be at all comfortable with.

And then the second thing is that given we're sort of going around the table, what's the acceptable risk? Maybe a formal decision analysis should be done.

DR. WEISS: Is there something -- do you have something that's going to add to this discussion?

DR. FERRIS: Well, I think so but others might not.

(Laughter.)

DR. FERRIS: You know, I said I was unimpressed with the preoperative cell counts being predictive. I am impressed by at least what I've seen that the postoperative cell counts did seem to be predictive as to who was going to develop edema. If you were down around 1,000, you were at risk.

DR. WEISS: Right.

DR. FERRIS: And then if you look at that

distribution, it's hard to know what the numbers are because I'm just looking at the scatterplot, but in my head I'm thinking 20, 25 percent are at risk.

DR. WEISS: It still gets back to that number, around 20 percent, 25 percent.

DR. FERRIS: Yes.

DR. WEISS: So we're still floating around the same.

DR. FERRIS: But that's another way of looking at the confidence interval. You know, that group is at risk. The others that are 1500, yeah, of course, they could develop it but probably not.

DR. WEISS: 1b and if we can get this, you know, sort of fairly quickly. Specular microscopy data, do they provide sufficient characterization of long-term ECD trends? Dr. Matoba said maybe not, but that's as good as we have. Is that --

DR. MATOBA: Well, I think even in the best of circumstances, when you have studies and there's one testing center and they do all them and there's one observer, there's at least a 10 percent variability. So it's not a very good way to, but I don't think there are very many other options.

DR. WEISS: Any other differing opinions? Otherwise, that --

DR. FERRIS: Actually I think they're great. They show that there's a big dip postoperatively, and then after that, they slowly decline, and that's about all you can say from it. So with time, they're going to go down, and where you are after that dip is where you are in terms of your risk over the next decades.

DR. WEISS: Well, probably I think you're both saying the same thing. They are sufficient enough for this study to evaluate what we need to evaluate.

So we're going to go onto question 2. This sponsor has constructed two grids for determination of a minimum preoperative ECD for various age and gender groups. Both grids are based on calculations assuming an end-of-life ECD of 750 cells per millimeter squared. Is the assumption of an end-of-life ECD of 750 millimeters squared acceptable? If not, what do you believe is appropriate?

Is this acceptable? Dr. Musch.

DR. MUSCH: You know, in a previous life or early on in my career, I did a lot of specular work with corneal transplants, and I was amazed how many crystal clear corneal transplants there were with a level much less than 750. And any number you're

going to choose, some people are going to have opacities and most won't. But it's really the corneal reserve capacity which is what you can't measure. That's important here, and it places a subject at risk of, well, if they get a stick in their eye or something, they're not going to -- the cornea is going to decompensate, and you cornea people know this much better than I. So I think 750 is a reasonable target to use for end of life.

DR. WEISS: Does anyone on the Panel disagree?

So I think there's agreement that that assumption is acceptable.

Going onto 2b. One grid is based on the ECD changes in a sub-cohort of 112 eyes, guttata-free eyes with anterior chamber depth greater or equal to 3 millimeters. The other is based upon the ECD changes seen in the full cohort of 206 IMT-implanted eyes. Please discuss which grid is appropriate as a contraindication for proposed patient population.

So if we had to choose between one of those two grids, would you prefer to have the entire IMT-implanted eyes and a minimum endothelial cell, and I think that was there higher endothelial cell counts, or would you prefer to have the grid saying have only

enrollment or we suggest only enrollment of guttata-free eyes with an anterior chamber greater or equal to 3 millimeters? Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: So just to lay out for the Panel, I know there's been some discussion of whether the idea of the grid is optimal at all. So I'll defer that, but, you know, in terms of the estimation of the guttata-free grid, there's sort of a spectrum of things that might have been done. One might have been a total data exploration where guttata sort of popped out of the analysis with no a priori, you know, biological justification. In that case, then the estimate of the quantities in the guttata-free population could well be quite biased, you know. On the other hand, if it was totally biologically motivated a priori, then we would put a lot more confidence in them.

I think we're somewhere in between. I don't know quite where in between, but my own assessment is that guttata-free grid may be -- I would not be surprised if it was anti-conservatively biased if you were to go and reproduce it in another population. It's hard to say, but I don't have a great deal of confidence.

DR. HILMANTEL: Slide 61.

DR. WEISS: So we're just asking to put up slide 61. Yes.

DR. HILMANTEL: Can I just make a clarification?

DR. WEISS: Yes.

DR. HILMANTEL: The question is not asking about the appropriate indication for the device. The question is only asking about which grid to use for contraindication, and the two grids are calculated based upon two different cohorts, but it's not a question about the indications for the device.

DR. BANDEEN-ROCHE: So the longwinded answer boils down to I have more confidence in the overall grid.

DR. WEISS: The overall grid being?

DR. BANDEEN-ROCHE: Meaning --

DR. HILMANTEL: B.

DR. BANDEEN-ROCHE: -- B.

DR. WEISS: Okay.

DR. BANDEEN-ROCHE: But just from an accuracy point of view, but I know there's other things that are being considered.

DR. WEISS: Dr. Matoba.

DR. MATOBA: Well, I would agree with Dr. Weiss' earlier comments that B seems unrealistic.

DR. WEISS: And actually my comments -- B is unrealistic, but I also agree that it's probably more accurate because A is based on 33 patients and I don't, you know, to go from 200 to 100 to 33 is a very -- is A based on 33 or 112?

MR. HILL: Allen Hill. Yeah, it's based on the cohort of patients non-guttata ACD greater than 3, and it's on approximately 100 patients.

DR. WEISS: So that's the 100 because that's not done by the corneal surgeons?

MR. HILL: Yes, ma'am.

DR. HILMANTEL: That's based on 112 patients.

DR. WEISS: Well, then I would defer to you, Dr. Bandeen-Roche. Is that -- 112, would that still be not accurate or --

DR. BANDEEN-ROCHE: So in my mind, I'm not as concerned about the precision as I am about the accuracy, and so, you know, it's really the method by which that 112 was arrived at as a secondary analysis.

DR. FERRIS: Can I ask a question?

DR. WEISS: Dr. Ferris.

DR. FERRIS: Yeah, Rick Ferris. It looked to me, and I don't have all this data within me yet,

but it looked to me that the preoperative cell count was somewhat predictive, but it wasn't that predictive. As a risk factor, you know, we talk about risk factors all the time. Smoking is a risk factor. This is kind of a moderate risk factor, but to hang everything on this one risk factor doesn't seem reasonable to me. It seems reasonable to me to say, all right, if you have a count of 2,000 or 1,800 now, you're at a little bit more risk than someone else. If you have guttata, you're at a little more risk than someone else. If Irving Schmendrick down the street who's never done corneal surgery before is doing this operation, you're at a little bit more risk.

DR. WEISS: You're at a lot more risk.

DR. FERRIS: And it seems to me that that needs to be --

DR. WEISS: We can put him in labeling as a contraindication.

(Laughter.)

DR. FERRIS: That's what, that the patient needs to know, that they're at more risk if their cell count is lower, they're at more risk if they have guttata, they're at more risk if you haven't done this procedure a lot before. I don't know how

you get that on the label, but it seems to me that it's a risk factor, and I don't think it's strong enough that you could make a grid and say you should do it in this patient and not in another. That's just my opinion.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: I just wanted to bring the Panel's attention to the fact that constructing an ECD grid as a baseline measurement of ECD needing to enter a study in general is not a new concept. As a matter of fact, that is the current contraindication for both phakic IOLs that are currently on the market, and it's now in the ISO standards which is not addressing directly the point that Dr. Ferris is making. I just wanted to make that comment that we have used grids as contraindications, and they are part of our standards.

DR. WEISS: And I would also say that we have to choose between one of these. Or I'll ask you to choose between one of these, and I will point out at age 75 and above, they're virtually identical. So we're really looking at the age 65 to 69 where B may be more precise and yet probably you won't get any patients with that endothelial cell count. So if you want the more precise one, I would presume you would

probably be starting at age 70 because you could still enroll people with that cell count, maybe 2195, you'll find a 70 year old with that for the B alternative, but I don't think you'll find a female with 3200 cell counts in the 65 to 69 category. So we might be -- if you wanted B, it's possible the 65 to 69 would be taken out of there because you're not going to find any patients meeting that criteria. What do you -- Alice.

DR. MATOBA: I think the numbers for B are unrealistic, and so I don't know if A is better, but I think it's more realistic. It's too stringent.

DR. WEISS: Dave.

DR. MUSCH: This is Dave Musch. It would help me, clarify things for me if I knew that this was an absolute contraindication that would subject a surgeon to some sort of legal action, or is this guidance? Because I think Rick mentioned a long time ago this morning that he would prefer that a surgeon tell him, well, here's the likelihood of loss and here's a grid that shows it, but given your situation, you make the judgment.

DR. WEISS: Well, what could happen is we could say it's an absolute contraindication or we could say a relative contraindication, or we can say

that we deem you at higher risk for corneal edema and potential corneal transplantation if you do not meet these endothelial cell requirements, although it will be up to the individual doctor and the patient to have that discussion. We can put it any way we want in the labeling, but the FDA would like to know which of these grids we would include. Malvina, do you still want to comment or did that -- yes.

DR. HIGGINBOTHAM: Well, if that's the question at the moment, I mean my choice would be A, I mean just because it allows us to entertain more candidates for this procedure, and to go into more limiting framework, I think, would not do the patient population for whom this is aimed at any service.

DR. WEISS: Now would you -- Dr. Bandeen-Roche commented she's not sure of the precision that A is based on.

DR. HIGGINBOTHAM: Eve Higginbotham. I'm not really sure if this is so scientifically driven that we know for sure. I mean if you can lose more than half of your cells and still have a clear cornea, I don't know why we're quibbling over 500 cells plus here. At the end of the day, we want to make sure that patients have the benefit of this procedure.

DR. WEISS: Well, I think we're quibbling over it because if you look at when you hit the 750, you'll hit the 750 earlier on one than another, and that will be before and perhaps necessitate corneal transplant because of corneal edema under the calculation, depending on which one you look at. Malvina.

DR. EYDELMAN: I just wanted to reiterate something Dr. Weiss said in a little bit different words. Whatever contraindications we put in the labeling, the surgeon can always pick a patient as a practice of medicine and go beyond the labeling if there's an individual patient for whom he or she decides it's warranted. And I think that's where the discretion is.

DR. WEISS: Janet.

DR. SZLYK: If this is meant to guide the patient and their doctor, shouldn't we take the more precise model and use the one -- I mean there are so many assumptions here. At least we know that model B is more precise.

DR. SUNNESS: So I must say that I'm concerned that the grid may do more harm than good in any case, and I hope people will argue with me, but, you know, we're talking about long, long

extrapolations here and, you know, in either case, there's a lot of model assumptions. We have the fact that the pre-ECD doesn't really well, you know, predict what the outcome will be after the surgery, and it's just the act of putting something like this down on paper, even if we sort of say, oh, this is just a guideline, you know, it tends to be reified. People tend to then believe, oh, this is really supported by strong scientific evidence.

DR. WEISS: Would there be the potential to have both grids and say that we don't know which one will be whatever?

DR. SUNNESS: It's a little confusing.

DR. WEISS: Or maybe no grid as opposed to everything else we're discussing. Dr. Edrington.

DR. SUNNESS: There are --

DR. EDRINGTON: Go ahead.

DR. SUNNESS: That there's not -- the information is, you know, again based on a number of different assumptions and that another way to go would be to say endothelial cell count should be more than 2,000 and forget about the grid because the fact of the matter is that from 70 and up, it's basically 2,000 anyway.

DR. WEISS: Well, I think the issue is

really in my opinion the 65 to 69-year-old group because if you want to have a more accurate one or the one that we are more sure it's accurate, I shouldn't say the more accurate, the one that maybe we suppose it's more accurate, you would probably not have many patients meeting that criteria.

DR. FERRIS: So that number almost surely came from not many patients, and I would love to see the confidence interval around that number because I suspect it's quite broad. I mean there's some goofy things going on here with women needing a whole lot more than men, and I mean it could be true. It's just --

DR. MATOBA: They live longer.

DR. FERRIS: What?

DR. MATOBA: They live longer.

DR. WEISS: Well, that's goofy.

DR. FERRIS: And there is one other thing. If you had this grid, I would want to make sure that the patient who happened to have 2,200 didn't get the wrong idea that, oh, thank God, I don't have to worry about edema because I don't think there's the evidence for that.

DR. WEISS: Dr. Edrington.

DR. EDRINGTON: I believe there's a grid in

between, correct? I mean one of these is based on sample size of 33.

UNIDENTIFIED SPEAKER: No, 112.

DR. EDRINGTON: 112, okay.

DR. HILMANTEL: No. This is Gene Hilmantel. There's no grid in between. There was one grid proposed by the sponsor, which is A. It's not so much a question of precision and sample size as it is that there's a question of possible bias in selecting the sample. The subgroup was selected after the study results were all in. So there's a question of possible bias in selection.

DR. WEISS: So I don't know if there's a way to put the phrasing use B, but put the phrasing to couch it and that this is based on a predictive. It has not been tested, or couching it so that if a patient came in who was 65 years old who had a 2600 cell count, and they had it done and they got corneal edema, it wouldn't put the physician in the position of a malpractice suit because it was suggested they didn't do that patient. So I don't know if there's a way to do that terminology or there's not.

UNIDENTIFIED SPEAKER: When you're doing a contraindication, it basically defines the patient population for which the device is approved which

means that anything other than that group, the patient, the physician, as a matter of their own judgment.

DR. WEISS: Ms. Niksch.

MS. NIKSCH: Barbara Niksch. So again the reason why the sponsor picked A was again to align with the whole risk mitigation plan that they put in place to define this for use in guttata-free larger ACD, et cetera. So I know it's a subset of a population, but it's directly related to who the sponsor would then be indicating the device were used with. So it would be the most relevant population.

DR. WEISS: The difficulty is it's an after the fact, and if it was prospective, I think we'd all invest in it, but being retrospective casts it into doubt, I believe.

DR. FERRIS: Can I ask the cornea experts here, is there -- Malvina, were you suggesting there is some grid for intraocular lens?

DR. EYDELMAN: For the phakic IOL.

DR. FERRIS: Phakic IOL.

DR. EYDELMAN: Right.

DR. WEISS: Did the sponsor want to make a comment on this?

MR. HILL: As it relates to labeling, I

want to suggest to you there may be other alternatives to contraindication. Warning may be appropriate also. So there are other avenues rather than strictly contraindications, listening to the conversations, that you may want to consider.

DR. WEISS: I don't think we're reaching a conclusion on this one.

DR. EYDELMAN: Please move on.

DR. WEISS: Let's move on. One more comment.

DR. BANDEEN-ROCHE: I mean just one other thing to keep in mind in thinking about this is that the criterion that was used, if I'm correct, was expected life. I mean so that these were the starting values such that the mean were plus a confidence limit would not cross the 750 threshold by the expected end of life, but that still leaves a substantial proportion, you know, who then outlive their expected. So I mean it's just one more, you know, issue about this grid to sort of keep in mind, about communicating risk to the patient.

DR. EYDELMAN: Again, this parallels how the grids have been done in the past.

DR. WEISS: If it's okay with FDA, we're going to move onto question 3, and the question 3 is,

in an attempt to identify the characteristics of a subgroup with an improved safety profile, the sponsor performed multiple subgroup analyses. Considering the statistical issues associated with these analyses, please discuss whether the data constitute valid scientific evidence for evaluation of safety of this device.

So there were multiple groups, different denominators that came from the second study. Does the data constitute valid scientific evidence for evaluation of safety of this device?

Dr. Higginbotham.

DR. HIGGINBOTHAM: Eve Higginbotham. It sounds like it's a continuation of our previous discussion related to ECD, and it's such a broad question, I think in general we've heard from the statisticians and the epidemiologists, the purists among us that, no, it's not solid scientific evidence. So that's the answer that I'll have to yield to, but we have to look at some practical issues, too.

DR. WEISS: Any contrary views, or would the Panel agree that it would not be? Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: I mean so just to

clarify, I mean the two issues of the different denominators, I think that we've already voiced that we're not satisfied with how those different denominators have been handled and what we've seen, you know, things like life tables or, you know, time to event analyses being needed. So that's one point.

In terms of the sort of multiple cohort analyses, I think this is the same point that I was trying to make with respect to the previous question, that, you know, it's very hard to say, you know, that we seem to in between a pure post hoc, let's look at every variable under the sun, and here are some scientifically motivated, you know, commonsense things to look at, and in terms of where of we are in between that spectrum, that's part of the issue.

DR. WEISS: Dr. Schein.

DR. SCHEIN: If I may, to address Karen. I think if you ask any of the corneal specialists on the Panel whether the presence of corneal guttata was likely to be a biological predictor of corneal swelling, you would be a unified response, similarly the depth of the anterior chamber. So I think these are not things that are generated by a statistical fishing expedition.

DR. BANDEEN-ROCHE: Could I just follow up

and just -- I mean so in -- and tell me, is this appropriate protocol to engage in? I mean and so, you know, evidently they were not things that were in the plan to evaluate a priority, and so, you know, given that, sure, after the fact, they make a lot of sense. I'm just trying to get a sense of that, you know, where we are on the spectrum.

DR. SCHEIN: Right. Again, it's a case series. There were no plan to do -- sample sizes were known straight going into the study, but imagine that you found a drug that had 100 percent effectiveness in men and 10 percent in women and you didn't know that ahead of time. It might change how you would label and advise application, even though it was a post hoc analysis.

DR. BANDEEN-ROCHE: Absolutely, I would agree.

DR. SUNNESS: You know, I think when we had the discussion about question 1, we were willing to accept a fairly large risk of cell loss or corneal edema. The difference, if you look at for example the guttata versus the non-guttata group, it's not so large so that in the chronic loss biexponential model, for example, you're talking about the chronic rate of loss of 4.8 percent in all and 3.8 percent in

guttata free with a 90 percent confidence interval even closer because there were a few patients.

So I don't think it's not really -- I don't think it's a big issue.

DR. WEISS: So the differences are not so impressive as to have to accept a group with a different denominator of the subgroup.

DR. SUNNESS: Right. I mean I don't think the fact that they did subgroup analysis would not have changed, or if they hadn't have done it, it probably wouldn't have changed what we were doing.

DR. WEISS: So I'm hearing consistency among the Panel members that they do not think the data from the subgroups are valid scientific evidence for evaluation of safety of this device.

Dr. Bandeen-Roche and Dr. Ferris.

DR. BANDEEN-ROCHE: I think that states my opinion too strongly. I mean to say that it's not valid, you know, I --

DR. WEISS: Can you state it in the terms that --

DR. BANDEEN-ROCHE: So I believe that the analyses that evaluate risk with respect to guttata and, you know, these other things that we've talked about are usefully informative. They're absolutely

usefully informative. And in terms of the overall findings, I think dovetailing with what Dr. Sunness just said, you know, I think that to the extent that they go short timeframe and, I mean not short but, you know, not decades, four year timeframe or whatever, that we have some reasonable data, you know, on the risk and the ECD trends. My only point here goes to the extent of the accuracy of the actual characterization of the ECD trend in the subgroups which could be somewhat biased.

Does that mean that the data are entirely invalid as evidence of safety and efficacy? I don't believe so. I think they're usefully informative. Do they provide an absolutely accurate estimate? Probably not.

DR. WEISS: I would convert that to saying it's not valid scientific evidence, but I'm not a statistician, which is not to say it's not helpful. It's helpful because we don't have anything else, but from a statistical standpoint, this would not be valid scientific evidence.

DR. BANDEEN-ROCHE: So I've already said that I put more faith in -- I consider it stronger evidence, the analysis that was based on the whole cohort.

DR. WEISS: Dr. Ferris.

DR. FERRIS: I was going to say a similar thing. I don't even know what valid scientific evidence means, but some things are more valid than others, and I would go to what David said earlier. You've got very nice estimates for two years with almost everybody followed and those are risk factors, and so that evidence is pretty strong. It's consistent over the next two years, as near as I can tell. So that evidence is consistent with the previous evidence. So it's not a randomized clinical trial of 4,000 patients. It's a case series of a couple hundred patients. It is what it is, but I wouldn't say that it's not valid.

DR. WEISS: Well, Dr. Eydelman has a comment, and also the FDA and the government in all its wiseness has a definition of what scientific evidence is.

DR. EYDELMAN: Well, this goes back to Dr. Ferris' question. Valid scientific evidence is needed for the data to be used for approvability of the device. So basically what we're saying is, is this data okay to be used as the basis for decision making? I don't know if that helped or confused you more.

DR. FERRIS: Not just the corneal thickness stuff but for the device overall?

DR. EYDELMAN: Right.

DR. WEISS: This is the definition.

MR. SWINK: You get this twice today. Valid scientific evidence as defined in 21 C.F.R. Section 860.7 is evidence from well-controlled investigations, partially controlled studies, studies in objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is a reasonable assurance of safety and effectiveness of the device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety and effectiveness.

DR. WEISS: Dr. Higginbotham.

DR. HIGGINBOTHAM: Well, I'd like to amend my initial statement and say that I think this is valid based on the fact that these are well documented case histories, as one of the definitions

of valid scientific evidence as I heard you read that definition. So I do believe it can be used, certainly the evidence that corneal specialists make a difference, that having a shallow ACD makes a difference, and as well as a guttata.

DR. WEISS: Does that not bother you that it's an after the fact when -- if you ask a corneal specialist and the corneal specialist on the study that was not listed as a criteria before the fact?

DR. HIGGINBOTHAM: Well, I mean based on the broad definition as read, I mean so we can talk about I guess various categories of what's acceptable, okay. Based on what I just heard, this falls within that definition as presented.

DR. FERRIS: Yeah, I would turn what you said around and say if it turned out that guttata were protective or low endothelial cell counts were protective, then you'd say, well, there's something goofy about this dataset. The fact that the biologic plausibility when you do the analysis, the risk factors come out in the direction that you think they should come out actually I think improves the believability of the dataset.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: Just to clarify again, we're

asking about the dataset of the end after you eliminate all the cofactors, not whether the statistical analysis show correlation with biological factors.

DR. WEISS: So I'm hearing from the Panel now that they -- there's some consensus that the subgroups constitute valid scientific evidence.

Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: So I do concur in terms of the analysis of risk factors. I think that that is, you know, valid scientific evidence in the sense that we've defined it.

In terms of defining a grid within the subgroup, that we can stand behind with, you know, a high degree of confidence in the accuracy, it's something that's not sort of an ad hoc thing, then I would say no on that one point.

DR. WEISS: I'm probably the only one who doesn't think it's valid scientific evidence, but the consensus rules.

Please discuss question number 4. Please discuss whether the sponsor's adequately demonstrated the effectiveness of the IMT taking into account the analyses of visual acuity improvement in eyes with cataract removal without IMT implantation.

UNIDENTIFIED SPEAKER: So I think the -- I don't think there's a question that they demonstrated it relevant to those patients who just had cataract extraction with an implant. I mean it's .3 lines versus 3 points -- lines. My issue is they haven't -- I know this study wasn't designed this way, but they haven't demonstrated -- I mean the more compelling analysis would have been if somebody had low vision rehabilitation and then compare how they did with it and without it. But I don't think there's any question that they showed it for --

DR. WEISS: So that you do not believe that they adequately demonstrated the effectiveness of the IMT.

UNIDENTIFIED SPEAKER: No, I believe -- I would say I do believe they adequately demonstrated it in regard to without cataract surgery versus with, but I mean I think, you know, in an ideal world, it would have been done low vision rehabilitation versus implantation with low vision --

DR. WEISS: But what they have you believe is adequate --

UNIDENTIFIED SPEAKER: Yeah.

DR. WEISS: -- to show that it's not the cataract --

UNIDENTIFIED SPEAKER: Right.

DR. WEISS: -- that's doing it.

Dr. Edrington.

DR. EDRINGTON: The 3.4 lines of improvement, to me that's sort of vague. I mean I don't know how much that actually helps each individual patient, but to me, the compelling thing having to do with vision is the visual function questionnaire and the results on that. I mean to me that's the most compelling thing about the vision.

DR. WEISS: But did they have that visual -- I don't recall. Did they have a visual function questionnaire? How would you, in the cataract eye versus the non-cataract eye?

DR. EDRINGTON: No, no. I'm just saying if you're looking at support for vision --

DR. WEISS: This question is just related to the cataract.

DR. EDRINGTON: Just asks about the cataract.

DR. WEISS: Just about the cataract. Was the --

DR. EDRINGTON: Strike that comment then.

DR. WEISS: -- improvement to vision related to taking out the cataract or was it related

specifically to the IMT device? Are we convinced that it was specifically IMT device and the cataract was not a confounding variable?

DR. HIGGINBOTHAM: Yes.

DR. EDRINGTON: Yes.

DR. MUSCH: Yes.

DR. SZLYK: Yes.

DR. WEISS: So I hear yes from Dr. Edrington, Dr. Higginbotham and Dr. Musch, and Dr. Szlyk. Are there any nays?

So I think the Panel's convinced.

Question 5, the sponsor has provided fundus images and investigator reports of fundus visualization performed by various techniques. Does this information support adequate visualization and treatment of the posterior segment of eyes implanted with the IMT? If not, please provide your rationale.

So can you look at the retina sufficiently after the IMT is implanted? What does the Panel think?

DR. HIGGINBOTHAM: Yes.

DR. WEISS: Dr. Higginbotham says yes.

DR. SUNNESS: Can we see some of the images? They weren't in our handout.

DR. WEISS: Can we see some of the images?

DR. HIGGINBOTHAM: Eve Higginbotham. It was the presentation actually.

DR. SUNNESS: Just that one slide.

DR. HIGGINBOTHAM: Just that one slide, but based on the -- this is Eve Higginbotham again.

DR. WEISS: Yes.

DR. HIGGINBOTHAM: -- executive summary.

DR. WEISS: I think it was .4 percent that were not visualized from my recollection.

DR. HIGGINBOTHAM: Four percent of the eyes --

DR. WEISS: Four percent that was not visualized.

DR. HIGGINBOTHAM: -- could not actually have these examinations done out of 1800 fundus examinations attempted. So that's the rationale for my answer in the affirmative.

DR. WEISS: And then they need to be something that would be put in labeling, too, as a warning in terms of patients who may be at higher risk for retinal detachment or retinal disease, that they should know that they may have more difficulty visualizing. Dr. Eydelman.

DR. EYDELMAN: Just to address Dr. Sunness' point. While we can't pull it up now, in your mail

out package, you did get samples of the visualization that you should have had access to.

DR. SUNNESS: I looked for it, and it said it was in -- anyway, I couldn't find it where I looked for it.

DR. WEISS: Dr. Higginbotham.

DR. HIGGINBOTHAM: Just as a follow-up to your last comment, it certainly doesn't preclude them from doing ultrasound that could further evaluate the status of the retina.

DR. SUNNESS: But, you know, I think we're fortunate now in the era of Lucentis and Avastin that even if in geographic atrophy at 4 years, there's about a 15 percent rate of getting choroidal neovascularization, but we no longer have to worry about being able to laser it.

So given the presence of -- it sort of takes the -- we don't have to image things as well as we used to have to. That's the bottom line.

DR. WEISS: Are there any other opinions on this particular question?

DR. FERRIS: So as a retina person, I wouldn't be thrilled with my view, but given the patient's situation, you do what you have to do and you can see something. You can't see as well as you

could otherwise see, and I think that's where you're left. And I agree with Janet, that you are going to have to worry about retinal detachment and choroidal neovascularization in these patients. Retinal detachment may be a lot more of a problem than mindlessly injecting Lucentis.

DR. WEISS: And so if you were going to put something in labeling, Dr. Ferris, what would you say to a prospective patient or what would you put in the labeling to the physician about the retina?

DR. FERRIS: That the fact that the view of the back of the eye is limited by the device to some degree, and it may somewhat increase your chance of a retinal detachment progressing for some time before you noticed it, it may make the surgery more difficult, but as long as the patient understands that there are some extra risks, I think that they're within a reasonable risk for the benefit.

DR. WEISS: Okay. Question number 6, the sponsor proposes the following indications and contraindications.

Indications. The Implantable Miniature Telescope is indicated to improve vision by monocular implantation in a patient 65 years of age or older with stable moderate to profound vision impairment

caused by bilateral central scotomas associated with end-stage age-related macular degeneration. Patients must have (1) retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography; (2) evidence of a cataract; (3) at least a five-letter improvement on the ETDRS chart with an external telescope; (4) adequate peripheral vision in the eye not scheduled for surgery; (5) willingness to participate in a postoperative visual training/rehabilitation program.

Contraindications. Evidence of corneal guttata, anterior chamber depth less than 3 -- I thought someplace else it was less than or equal to 3, so someone can correct me on that. The IMT is contraindicated in patients who do not meet the minimum age and endothelial cell density, as shown in the grid. And the grid they're using is the one with the lower endothelial cell counts. Additional list of contraindications are proposed by the sponsor in labeling, which is another amendment.

Please discuss whether the sponsor has provided reasonable assurance of safety and efficacy of the device for the proposed indications and contraindications. What, if any, modifications to

the proposed patient population do you recommend?

So first we're going to answer the first one. In terms of the indications as well as the contraindications, the contraindications again are the age, the endothelial cell density graph, the anterior chamber must be 3 or more, the evidence of corneal guttata, is there reasonable assurance of safety and efficacy for these indications and contraindications?

Who would like to tackle that one? You would like to tackle that one, Dr. Ferris. I can tell.

DR. FERRIS: Except for the fact that the grid and the statement that you have to be over age 65 don't seem to line up. Isn't there a 55 to 65 on that group?

DR. WEISS: Yeah. The sponsor seems to have taken out the 55 to 65.

DR. FERRIS: So I don't care so much about the grid anyway. I think they've shown that the device is effective, and I think they've demonstrated clearly that there are a number of safety issues that the patient has to be warned about, and under those circumstances, I think that that's my recommendation, that as long as the patients are appropriately

notified of those risks that I think have been clearly identified, I think it's fine.

DR. WEISS: So you would say --

DR. FERRIS: I would not --

DR. WEISS: If a patient is informed, it would be considered reasonable safety and efficacy.

DR. FERRIS: And I take it from what the sponsor said that that list of guttata and other things, none of those were contraindications. They were risk factors.

DR. WEISS: Now the way it's listed here though, it's listed as a contraindication. So they are listing it in their proposal as contraindications are guttata, are an anterior chamber depth less than 3, are patients who do not meet the minimum age and endothelial cell density.

DR. FERRIS: Well, far be it for me to force the sponsor to make the device more widely available. If that's the way they want to do it, that's okay with me. I think that that's overkill frankly from what I've seen but --

DR. WEISS: But their minimal ECD was the less conservative chart, and I suppose we have not really reached a conclusion one way or other which chart one would use. Dr. Matoba.

DR. MATOBA: So I agree with Dr. Ferris, that 65 -- I don't necessarily think that if you're 55, you should be denied an opportunity to consider having it implanted. On the other hand, we have to be careful that then someone doesn't say, oh, you're 25 and you've got a traumatic macular problem, but there's no age limit and maybe you should have it. I mean so if we can make sure that it's going to begin at least to be implanted within the people with the age-related macular degeneration, older patients, then I think we could liberalize the numbers a bit and have young patients, in their fifties.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: Well, it's currently proposed for 65 and above.

DR. MATOBA: Yeah, but I'm thinking 55. I mean there might be some younger patients who would benefit, and they would be the more active patients who may want it more even than the older patients.

DR. WEISS: Well, I would say the difficulty, we can discuss that. I would say that would be a side issue, and the difficulty with that is, at least I would like to hear from the sponsor, how the patients did from 55 to 65, and we would have to expand that ECD grid from minimal numbers which

wasn't presented here, and we would want to know why that was taken out. So there are a lot of other aspects to that. We can revisit that if, you know, members of the Panel want to revisit that, but the more important issue I think for the sponsor and everyone here is just the majority of what the indications --

DR. FERRIS: Does this mean that what we're suggesting is this is the on-labeled use of this device?

DR. WEISS: This is the labeled use of the device.

DR. FERRIS: That's the on-labeled use.

DR. WEISS: Yes.

DR. FERRIS: People can use devices off label --

DR. WEISS: That does not happen, does it?

DR. FERRIS: It happened once when I was at Hopkins.

DR. WEISS: Okay.

(Laughter.)

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: If I can just point out that at the original Panel in 2006, as Dr. Lepri's slides indicated, the indication was 55 on, and then

subsequent to the analysis of the data, it was the sponsor's proposal to limit it to 65 and beyond.

DR. WEISS: The sponsor wants to comment on that. Mr. Hill.

MR. HILL: While I also don't like restricting indications, I believe it is prudent to restrict the device to age 65 and older. Our data was very limited on younger patients. They did, however, do well and their cell densities were quite reasonable, but it's a very limited sample. So I believe the restriction is appropriate.

DR. WEISS: Fine. Thank you for addressing that. Mr. Bunner.

MR. BUNNER: Not to be stuck on the eye rubbing issue, but I know going back into contraindications, we talked about the history of frequently rubbing eyes or any conditions that predispose a person to that. I guess my other concern about implanting this in our aging population is increasing weights of dementia. And so when you're advising patients as to their long-term prognosis, what am I at risk as a consumer, what am I at risk at if I'm suddenly facing dementia and I have this implantable device in my eye? I'm wondering if that's --

DR. WEISS: Well, typically in the labeling, there's a long list of contraindications, of warnings and such, in labeling for patients and labeling for physicians. Now, what I'd like to ask Dr. Eydelman is they do refer to an additional list of contraindications proposed by the sponsor in the labeling, Volume 2, Amendment 13? Do you want us looking at that, or is that something FDA will do because that's part of the labeling?

DR. EYDELMAN: We will do that if you have specific recommendations. You can certainly voice that, and we'll double check that they are included or excluded. But we have pulled the ones, the contraindications which were used to mitigate risk of endothelial cells from a long list of contraindications. That's why the question was presented as is.

DR. WEISS: So I guess this would be an area where if there's specific things that Panel members would want in the labeling to, and correct me if I'm wrong, Malvina, if there are specific things that we would like in the labeling to patients as well as to physicians, this would be a place to voice that.

DR. EYDELMAN: Yes.

DR. WEISS: So one of these things was the patients should be warned about eye rubbing, and I don't know if that's already in here. It may already be in here. It's already in there. Okay. So we would want that in there. So what we come up with may be a duplication of what you have because I can't read all the labeling here, but are there any other aspects? Dr. Higginbotham.

DR. HIGGINBOTHAM: Well, one of the comments I wanted to make, in that same line earlier, was that the patient needs to be able to give informed consent, I mean because there is a high rate of, you know, organic brain disease in this group, and so I can just see this going into patients because you don't know what patients are going to do once they're in that stage, but I also wanted to add a little bit more clarification on the AC depth. That's central AC depth that we're talking about.

DR. WEISS: Yes.

DR. HIGGINBOTHAM: So we might want to --

DR. WEISS: Say central anterior chamber.

DR. HIGGINBOTHAM: Yeah, central anterior chamber depth.

DR. WEISS: I have a great concern about how to ensure the patient gets informed consent

because how often does a patient ever see the labeling from the devices? Not frequently, and how often does the doctor see the labeling from the devices even though we cogitate a long time about it at the Panel meetings? And so the question that I would ask is aside from, and I know the FDA does not get involved in the purview of the practice of medicine for the individual patient, but I would wonder how the company could get involved in terms of the information given to the doctor to better ensure that the patient gets this incredibly important information about corneal decompensation rate because if it's treated cavalierly as anything else that happens with the device, and the patients do not get this information, then much of this deliberation will basically have been for naught.

DR. FERRIS: I think Eve's point about the ability of the patient, not to just give the informed consent, but also to do this training is really important, and I agree with you, that if there's some way to make sure that the patients, you know, document that they do they understand this, I think that's very important.

DR. WEISS: And I don't know that -- I mean and this is not done, but I personally would love a

consent form from the company that patients, that has been put together that patients get, and so you could be ensured that they actually see this as opposed to leaving it to the individual physician solely to basically have the information and know that, particularly because I would expect the corneal edema rate would go up in the population. Not all corneal surgeons may be at the level of the corneal surgeons in this study, and the other surgeons in this study, I assume were at a very high level, and they were not sufficient. And if the surgeons in this study were not sufficient, then what will happen with the corneal edema rate when you get it into the population where surgeons may not have that same level of skill?

So if the Panel is in agreement that we will be willing to accept something that did not meet the original safety guidelines the sponsor had set up, but it would be okay if the patient does get the information, how does one get the patient the info? And I don't know if the sponsor has any ideas on that. Yes.

Aside from teaching the docs in the course and having them go home and maybe or maybe not relaying it.

MR. HILL: Regarding recommendations for professional use and also for patient information, in the packages you received under Appendix 13 is a complete set of the proposed professional use information which includes all indications and contraindications regarding mental state of the patient, which I believe would address that information, and I believe we also have the patient brochure in here which is to be provided to each and every patient that may be a candidate for this device.

DR. WEISS: Well, here's a question. For many devices this is available. Patients don't get it. And I think doctors may have to pay out of pocket for it. I'm not sure. The doctors don't necessarily have these available. Is there anything that could be done to make this device different in terms of informing, making more sure or doing a better job that the patient is actually informed?

MR. HILL: As it relates to working with physicians who may be implanting this device or recommending it to patients, it would be implanted with advice. For implanting physicians, there is a required training program to certify which has been proposed and is in the labeling. As part of that

component and as part of our indication, we're also requesting in the labeling that the physician discuss the specific risks, similar to what Dr. Ferris mentioned, with each and every physician. So (a) physician training, (b) within the labeling requirement. I think that's the best way we can do that.

Can we go beyond that? We generally do not have patient contact, of course, but we would certainly make information available to potentially referring physicians regarding the completed patient information. So that's public domain, and that can be broadly distributed.

DR. WEISS: Is there a patient video that a patient would watch that could include this?

MR. HILL: That's certainly possible. There's information on websites. There's complete information there, and that is available in large text. Of course, that generally comes from patient relatives rather than the individual patients, but we concur that that should be considered, and we hope that if you'll take a look at the information in the proposed labeling, that that would be considered appropriate.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: Actually if you don't mind, I would like Dr. Bonhomme to comment on an informed consent was used on the device outside of the ophthalmic area that is very unique.

DR. BONHOMME: The product are the silicon gel breast implants, and there is an information packet that the physician must discuss with the patients, and they do document informed consent, and it is signed. So there's a precedent for this.

DR. WEISS: So I would step out of my position as Chair and maybe more in the position as patient advocate and ask that that would be included before I say that that's my own personal opinion, but what do other members of the Panel feel about that?

MS. NIKSCH: Barbara Niksch. Just to clarify, too, there are currently approved ophthalmic devices that already have patient information brochures. They're posted on the companies' websites. They're actually again promoted during the training of the physicians, given to them. They are instructed how to give them to their patients. They combine it with their own informed consent procedure within their practices. Beyond that, the sponsor, you know, obviously can't hand one to every patient, but this is generally common practice for a lot of

ophthalmic devices already, as you may know.

DR. WEISS: Yeah. Barbara, I've been on the Panel for a number of years, as you know, and I've been a physician for more years than that, and I can tell you there's what we would like and what happens. And what happens, as an ophthalmic surgeon, I've gone to some of the courses for devices that have been proposed here, and what gets said here and what gets said at the courses are sometimes two different things.

And in all good faith, I think everyone in this room, if this got approved, would want the patient to know. And so I think we need to do another step beyond the steps that we have that often patients don't get the labeling and often doctors don't read the labeling, and sometimes the person who might be teaching the course won't be saying what the issues were. So if there's something like this brochure that has been used for other things, that a patient would get so we could better ensure that someone who was let's say willing to accept a 30 percent risk of corneal edema, whatever the risk is, says hey, that's fine, I'll take it, it's important to me they got that information.

Again, that's my personal opinion, but I'm

going to defer to the Panel.

DR. FERRIS: Well, can we make a motion and vote on it. I don't know whether that's out of order but --

DR. WEISS: Well, we can include this in the labeling.

DR. FERRIS: -- I'm going to motion that this Panel recommends that the Agency follow up on that model that was used in breast implants for this device because it does have some extra risk attached to it.

DR. WEISS: If there's consensus in the Panel, Mr. Swink is scribing for me, and what we're doing is as recommendations are being made, we're writing them down, and that could be one of the conditions that is attached to this PMA. Are there any other comments on that? Any disagreement with that on the Panel?

Are there any modifications to the proposed patient population or any other issues in terms of particular concerns with indications or contraindications?

Dr. Eydelman, anything else on that question? Otherwise, we'll go onto question 7.

DR. EYDELMAN: Just indicate the answer to

the second part of the question.

DR. WEISS: Second part of the question?

DR. EYDELMAN: What, if any, modifications to the proposed patient population do you recommend?

DR. WEISS: So modifications to the proposed patient population.

DR. EYDELMAN: As defined by indications and contraindications. In those words, indications, contraindications, just as in Dr. Lepri's slide, define who is on label.

DR. WEISS: Does anyone want to have any changes to the population that this is proposed for in the indications or contraindications?

Dr. Bandeen-Roche.

DR. BANDEEN-ROCHE: So just -- and you can tell how torn I am over this minimum ECD table, you know, I mean. So just one thought to consider would be rather than extrapolating back from the end, you know, the expected end of life, one could set a reasonable number. I mean this was raised by somebody else, like 2,000 and then use the most data available to estimate the expected years forward from that point to crossing the borderline.

Now, I know this sounds like, you know, just a variation on theme, but to make it very clear

that this is an extrapolation, I don't know. I mean that's just one other approach that I think FDA might consider.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: That, of course, will negate the whole use of the life expectancy because as you see in the excerpt of the grid, for example, for 85 to 89, 1800 is the entry criteria, and given the population that was enrolled, most of the population was in that age group.

DR. BANDEEN-ROCHE: That's what the proposal would be.

DR. WEISS: Dr. Musch and then Dr. Higginbotham.

DR. MUSCH: Dave Musch. I'm as torn as Karen is about making this a contraindication when none of us feel that it is deified, as I think Karen said, and we would be doing that by establishing it, but on the other hand, if we don't say anything about a minimum endothelial cell density, then my concern is that people will be just putting it into anybody.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: Of course, one other option is to recommend that the contraindication table starts, let's say, I'm just making this up, at 70 or

75, and for the decade before, two decades before, make it as a warning which is not an absolute contraindication because that's the age group that I heard most of the issues was from 65 to 75.

DR. WEISS: Dr. Higginbotham.

DR. HIGGINBOTHAM: Well, my comment was on something else, but that might be a good compromise since there seem to be the greatest difference between version A, version B, in that 65 to 69, but my comment was actually related to potential contraindication. I saw it in the patient brochure that if you have uncontrolled glaucoma, why would I mention that, that, you know, you may not be a candidate or that's what I gleaned, and so uncontrolled glaucoma particularly given the fact that you're not going to get a great view of the disc, and certainly you're never going to get a good visual field, that that would be something to explicitly state.

DR. WEISS: And the sponsor's sort of nodding that that -- we'll scribe that, but I believe that's already in the --

UNIDENTIFIED SPEAKER: Yes, it is.

DR. WEISS: Okay. I would actually also add something. I think there's instructions on how

to do a YAG laser in here, but it's never been done. So it's never been done. I would just say it's never been done. You don't have to be the first if you're the doc reading this.

DR. HIGGINBOTHAM: And if I could, the compromise is actually very, very close to my proposal. I was not proposing to not have a minimum, you know, but I think I was reflecting my particular discomfort with the minimum it extrapolates, the farthest, and that is the most variable between the two analyses, and I think we've given probably enough guidance. I hope that FDA can then make a decision.

DR. WEISS: If no other comments on that, I just had a quick thing, and this is fairly trivial. The 2.2 versus the 3.3X, in one area, I saw they weigh different amounts, but in the physician indications, it shows they weigh the same. So whatever it is should be corrected to whatever it's supposed to be.

Question number 7, the last question. At the time of the July 2006 Panel meeting -- yes.

MR. HILL: Just one quick comment. I wasn't quite sure I understood the summation of that last point.

DR. WEISS: Yes.

MR. HILL: It's a very trivial point, just one of accuracy. Table 1 in physician's labeling, they talk about the weight of both models of the different telescopic prostheses, and they have the same weight. I thought in another area I saw that they had different weights.

MR. HILL: They're comparable. There's no material difference between the two.

DR. WEISS: Okay. Fine. So that's --

MR. HILL: And it relates to the point on the modified position. I wasn't quite clear where that ended up. Were --

DR. WEISS: You're in good company, Mr. Hill.

MR. HILL: Okay. All right. So whether it would be a warning or something like that with some minimum ECD which sounds like a reasonable -- let's call it some other labeling which sounds like a reasonable approach from what I'm hearing from everyone at the Panel versus the contraindications.

DR. HIGGINBOTHAM: Yes.

DR. WEISS: I don't think we've -- we have not made any determination.

MR. HILL: I understand.

DR. WEISS: I'm going to be guided by --

MR. HILL: I was trying to understand --

DR. WEISS: Yeah, we don't understand it either. So that's why you don't understand it.

MR. HILL: Okay.

DR. WEISS: Do you need --

DR. HIGGINBOTHAM: Can we outline it again perhaps and have the Panel weigh in on that?

DR. WEISS: Do you want us to continue this discussion?

DR. EYDELMAN: I just want to hear an answer to the last part of 6 before you move on.

DR. WEISS: Answer to the last part of 6. Any modifications to the proposed patient population?

DR. EYDELMAN: So is the answer no?

DR. HIGGINBOTHAM: Let's go around the table.

DR. WEISS: I think one question I'm going to -- we have not decided on which of the minimum ECD tables we have.

DR. HIGGINBOTHAM: That's correct.

DR. WEISS: That's clear after 20 minutes of discussing it. The second thing is now I think we're entering the question is it a contraindication or warning? Is that the question, Malvina?

DR. EYDELMAN: No, beyond that.

DR. WEISS: Beyond that. Is there anything else that we -- anyone proposes for the patient population or are we satisfied with the patient population that's listed? If we're satisfied with the patient population that is listed, we can go onto question 7.

DR. HIGGINBOTHAM: Madam Chair --

DR. WEISS: Dr. Higginbotham.

DR. HIGGINBOTHAM: -- there was at least a suggestion that perhaps we could take out the 65 to 69 age group.

DR. WEISS: In terms of the table of ECD.

DR. HIGGINBOTHAM: And place it as a warning but then go ahead and continue on with the 70 on as indicated.

DR. WEISS: Well, we can --

DR. HIGGINBOTHAM: That's a summary. That's a paraphrase of -- I myself concur with that as a recommendation.

DR. WEISS: So is there interest in keeping 70 and above as a contraindication and 65 to 69 as a warning?

DR. SUNNESS: I would simplify it just because again, as we've said a number of times, that I think this is -- it looks too specific, and we

don't have that much information. I would propose that it's an absolute contraindication 2,000 or less up to age whatever, 84, and then 1800 after, and then put the warning for, you know, for the 60 to 75 for the higher numbers.

DR. WEISS: As a corneal surgeon, I would play devil's advocate and say for the younger patients, it's even more important for them to have a robust endothelial cell count because they'll be around long enough to get the corneal edema. So I really wouldn't -- if you want to put a warning, I'd rather do it on the 90-year-olds who might not be making it to their postop visit, you know.

But I will defer to my -- group. Do we want to change any of it to warning or do we want to just keep it all as contraindication?

DR. FERRIS: Well, it's amazing to me that something that might have a relative risk of 1.4 or something is all of a sudden going to be a contraindication. If it was a relative risk of 4 or -- this is -- there was almost no evidence that there was such a high relationship, and I like the idea of the warning because the lower your endothelial cell count is, the higher your risk. There's no doubt about that. The idea that there's

some artificial cutoff to me is silly.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: Madam Chair, when I asked for an answer to the question, I was hoping to go beyond the grid to see if there was any other criteria.

DR. WEISS: Are there any other -- anything else besides the grid?

DR. FERRIS: Yeah, I think we all agreed that the --

DR. WEISS: Okay. Nothing else besides the grid. Do you want us to discuss the grid or go onto question 7?

DR. EYDELMAN: Please go on.

DR. WEISS: Go onto question 7. At the time of the July 2006 Panel meeting, the sponsor submitted protocols for two postapproval studies, a five year follow-up of IMT-002-LTM patients, a long-term monitoring study of IMT-002 patients and (2) a prospective multicenter postapproval study of the Implantable Miniature Telescope (IMT patients with central vision impairment associated with age-related macular degeneration, a follow-up study of newly enrolled patients who received the IMT after approval out to 5 years). On February 6, 2009, the sponsor

indicated that they do not believe a postapproval study is warranted at this point because most subjects followed in IMT-002-LTM have reached the four-year follow-up exam. However, to address the possibility that a postapproval study may be recommended, the sponsor submitted a protocol to follow some of the subjects implanted under IMT-002 for two additional years. There are four parts to this question.

So part a: Given the currently available safety and efficacy data, and if this device is approved, is a postapproval study recommended?

Could I just have a show of hands how many would like a postapproval study? We've got eight. So we have a majority of Panel members who want a postapproval study if my math is correct.

Okay. FDA, is that fine with you? We have majority, eight members wanted at postapproval study.

DR. EYDELMAN: Thank you.

DR. WEISS: We can go on, b: If a postapproval study is recommended, does the Panel agree with the sponsor's proposal to follow currently implanted patients to seven years? If not, what do you recommend?

Does the Panel want to follow the currently

implanted patients to seven years? How many would say yes?

DR. SUNNESS: As an exclusive thing or in addition to a separate PAS?

DR. WEISS: Well, that is the PAS from my understanding.

DR. FERRIS: She's asking or I'm asking, does that exclude something else --

DR. WEISS: Right.

DR. FERRIS: -- if you vote for that or could there be two --

DR. EYDELMAN: Dr. Bonhomme is going to --

DR. WEISS: Yes.

DR. BONHOMME: The seven-year study is the sponsor's proposal, but we are willing to entertain other options.

DR. WEISS: So we believe in least burdensome. So my supposition is we would not be saying go to seven years plus do something else. We would be choosing the best study. Is that a correct supposition?

DR. BONHOMME: You could --

DR. WEISS: We can do anything we want.

DR. BONHOMME: -- do both or one or you've already decided that it wouldn't be none. So --

DR. WEISS: What do -- Alice.

DR. MATOBA: Well, I have one issue, and I would like to know what the Panel thinks of this is that I have some concerns about the intraoperative problems that can arise, and if we now start having everybody doing it, then we don't know whether all of a sudden there will be a big jump in the number of intraoperative problems, and that's one aspect that I'm curious about. That would be a different type of study.

DR. WEISS: So I would agree with Dr. Matoba is once we reach the normal population and we have all surgeons do this, even corneal surgeons who maybe are not as well trained or not as skillful, and people who are also not used to large incision surgery, are we going to have a higher rate of endothelial cell loss, corneal edema, choroidal hemorrhage --

UNIDENTIFIED SPEAKER: -- loss, whatever.

DR. WEISS: -- loss, yes. Oliver.

DR. SCHEIN: Thank you. Oliver Schein. I want to make a point that I think it's far more valuable to get a little bit of key clinical information on large numbers of patients who are newly enrolled in the setting in which the product

will be actually used rather than more detailed information, things like endothelial cell counts, on an ever dwindling population. This population is old to begin with, the numbers that are going to make it to seven years is very small, and you're not going to get at the information that you want from a public health perspective.

So my view is that if you can capture things like explanation, need for corneal transplant, and/or loss of vision attributed by a surgeon to corneal edema, then you would have captured the most important things, and to do this on a prospective basis in a larger sample.

DR. WEISS: So you're not supporting the original proposal of the --

DR. SCHEIN: Am I personally supporting it? No.

DR. WEISS: Do you have your plane ride back home?

DR. SCHEIN: Luckily I have a car here. So, as you can tell, I'm not actually involved in those earlier submissions, but it makes no sense to me.

DR. WEISS: Okay. So you're suggesting don't follow them to seven years. Enroll a new

cohort of patients and prospectively follow them.

DR. SCHEIN: Something that gets at the key indication, the key issues. One quick analogy, there was postmarket surveillance study I was involved with about three years ago with New Generation extended wear contact lenses. The question is, do they have a higher infection rate? So you chose the most important outcome. In that case, it was clinically documented microbial keratitis, and you get a very good answer for the most important set of circumstances, not surrogate outcomes like cell counts and pachymetry and so forth.

DR. WEISS: What do members of the Panel think? Dr. Musch.

DR. MUSCH: Dave Musch. I'm very supportive of what Dr. Schein just recommended, and it really goes into item c where we're asked to talk about a new PAS rather than what is proposed.

DR. WEISS: So if there is interest in enrolling new patients, looking at them prospectively, looking at such things that have been mentioned as need for corneal transplant, explantation rate, would members of the Panel want the currently implanted patients to be followed to seven years or no? Dave, follow them or not?

DR. MUSCH: I, you know, I don't know how we weigh in on the burden to the company, but I don't know where seven years came from. I would envision a sufficient sample size study in which you follow perhaps 500 patients for 5 years, and given the death rate of this group and all that, if you end up with 300, I would be feeling pretty happy.

DR. WEISS: But we didn't start with 300. So --

DR. MUSCH: Well, starting with 500 or whatever number is factored in so that you have a sufficient number at five years to --

DR. WEISS: We're talking about the prospective. Are you talking about the prospective?

DR. MUSCH: Correct.

DR. WEISS: I'm going back to the seven years. The original proposal of the sponsor was to follow the currently implanted patients up to seven years. So would you want to follow the currently implanted patients or no?

DR. MUSCH: No.

DR. WEISS: No.

DR. MUSCH: Because most of those patients don't even meet the indications that we have just talked about.