such as wearing ball caps, sunglasses, things like that, which is I think typical for many populations, but the primary reason for requesting explant was glare or sensitivity to glare.

Second was the group that had Stargardt's. Stargardt's macular dystrophy who were enrolled in the trial, there were only six of those. Three of those, of course, requested explant. Those particular patients, as Dr. Peli had mentioned, preferred to have the means of let's call it turning on and turning off the device. They were very comfortable with external devices, and that plus the addition of glare was the reason for explant.

Regarding postoperative ECD, I would like to pull the tables up for you to provide that. I think I can say without hesitation, there was nothing dramatic about the loss of ECD post those procedures, but I'll provide the exact numbers to you.

DR. MATOBA: Okay. Did other patients have glare say to a milder degree --

MR. HILL: Yes.

DR. MATOBA: -- after implantation?

MR. HILL: Yes.

DR. MATOBA: So it's something normally discussed with the patient before the --

MR. HILL: Yes, we discuss glare in their training process, to learn to use the device postoperatively. We recommend just various glare mitigation things, very simple straightforward things. Wear a ball cap when outside, wear sunglasses, very simple things.

DR. LANE: Steve Lane. One of the patients was a patient of mine that was explanted, and while the patient did indeed have a glare, it was also in this patient an issue with the ability to use the telescope as essentially the central vision modulator in one eye and the peripheral vision in the pseudophakic or phakic opposite eye, and this patient just was not able to mesh that so that they could be comfortable being able to use the eye in that way, something we train patients or in trained patients with preoperatively with an external telescope, but it just shows you that sometimes what happens as you try and prepare and set up a patient for this, that it just doesn't work, but in that case, that was probably the main thing that led to the explantation in that patient who was very much more satisfied following explantation and placement of a standard lens implant and have the peripheral vision ability in both eyes and was a happier camper.

DR. MATOBA: Okay. My second question is Dr. Stulting's presentation on the intraoperative complications. Was your data for both the IMT study and the LTM study or just one? Because just looking at this table that was provided to us beforehand, where the two studies are listed separately, with the intraoperative complications, and there's at least one suspected or actual choroidal hemorrhage for each of the two studies, and then the rate of patients requiring retractomy, the total numbers are higher than what was in that one table that you listed.

DR. GORDON: Judy Gordon. I'm going to answer this question because it just relates to often how we report adverse events and studies, where those patients had that event intraoperatively, and as they continued through the study, it continued to be reported but those were not new events. So they were existing events. They show up again --

DR. MATOBA: Oh, okay.

DR. GORDON: -- because of the nature of the tables.

DR. MATOBA: Okay. But then there was one in the IMT study and one in the LTM study that was listed as choroidal hemorrhage, and I thought that that was a very high rate of choroidal hemorrhage.

DR. GORDON: We'll confirm, but I think it's the same --

DR. MATOBA: It's the same patient.

DR. GORDON: -- same patient.

MR. HILL: It is the same patient.

DR. GORDON: It's really a reporting artifact. That's what I wanted to come up and explain.

DR. WEISS: I also had a question in terms of the surgical complications. In the four patients who came out to corneal transplantation, I think, Doyle, you had reported that most of them had iris prolapse. What was the rate of iris prolapse in other patients? I mean what was the percentage of patients who didn't have -- go onto corneal transplantation who had iris prolapse?

DR. STULTING: Doyle Stulting. We'd like to take a moment to get that data, to get those data for you. There was something else that I wanted to say, but it left me.

DR. WEISS: I'm just trying to sort of simply get more of a handle on, once you get iris prolapse, is that a defining characteristic that this patient has a much higher chance or was it a random event that occurred in many patients and happened to

also occur in these patients? Yes.

MR. HILL: Dr. Weiss, Allen Hill. There were 12 reports of iris prolapse in the IMT-002 study. That's all eyes.

DR. WEISS: So there would be 8 out of approximately 180 that didn't have --

MR. HILL: Yes, that's 5.5 percent, and a portion of those eyes did have iris prolapse that had the transplants. I'll get you the exact --

DR. WEISS: So one-third of the eyes that had iris prolapse went onto corneal transplantation?

MR. HILL: I'll verify that number.

DR. WEISS: David.

DR. MUSCH: Dave Musch. I'd first like to address a comment that Dr. Peli made about astigma and maybe give the sponsor or Dr. Peli an opportunity to expand on that a bit. And I'm looking at the visual function questionnaire findings and note the impressive improvement in some of these visual functions of daily life, and I want to respect the people that came here to speak on that, too. It's quite impressive, but obviously it's their anecdotes, but this supports it from the study.

I wanted you to comment on or redirect your attention to several of the other scales and maybe

expand on it a bit, and those scales are dependency, mental health, and social functioning. I found those to be as impressive as the ability to read fine print. Could you comment on that from a low vision perspective?

DR. PELI: Eli Peli. Sure. I think this is crucial. The social one would be included that as a low vision practitioner, you frequently hear from these patients the complaint the inability to recognize people or to interact with them appropriately is a stressful event in their daily life, in their senior citizen housing. If you don't greet people at the appropriate time, at the appropriate distance, you may run into some social issues. So it is really an important issue that's undermined and therefore help significantly.

The other items that you mentioned, such as independence, have to do with the fact that indeed we think that intermittent distance activities are important and the patients have that, but I think there is a measure of just getting more confidence, which you've seen in the anecdotal presentation, that once people are able to do a few tasks, then their whole outlook is changing and may affect their independence in a way like this.

DR. WEISS: Yes.

DR. SUNNESS: Janet Sunness. I had a few other questions just to give me a sense of how patients adjust with this and some practical issues also. First of all, once you implant the lens, do you have to do any distance refraction? I mean in other words, do you just take it as it is?

DR. PELI: No, you do have to do refraction and you do have to provide the glasses. It's not enough to give patients the --

DR. SUNNESS: The telescope.

DR. PELI: -- script and expect that -- yeah. It's not that you have to make the glasses but you have to somehow have in your process of follow-up, verify that at least the next time they have the glasses. The interesting thing is that the improvement, even in a fairly large dioptric corrections of say three diopters which you would expect, is not as dramatic as you would read off from a regular table. Possibly a pinhole effect, there is a larger depth of field as I said from one and a half to infinity is really the depth of field. So this has some kind of a pinhole effect which helps in that regard, but some of the patients need more than that and some have astigmatism with this kind of surgical

procedure as you'd expect, and that is important to correct.

DR. SUNNESS: And would you know offhand, I mean were there a lot of weird refractive errors that came out after this?

DR. PELI: I don't know. I haven't seen the data on the refractive error, but the few that I've interacted with and that I've measured myself, that I refracted myself, there were a number with three diopters of astigmatism, even four. And I don't see that as a surprise with that kind of surgery, and I have been hammering on that.

MR. HILL: Regarding were there any weird refractive errors that we had to address, the answer is no.

DR. SUNNESS: Okay. My next question is I understand in the group that was worse than 20/80 or -- well, actually let me back up. The ones, the eye was selected, if I understand it correctly, if they were in the better acuity, it was selected as the worse eye, and if they were in the profound acuity loss, it was at the discretion of the surgeon and the patient. So what I was wondering is if you came across any findings from that that would give guidance to physicians who were choosing, and also in

terms of adapting to the disparity between eyes, if that was a significant issue in terms of which eye was done.

MR. HILL: Allen Hill. I'll try and handle the first part regarding adaptation. I will rely on Dr. Peli. You are correct in terms of the protocol. The protocol required that if visual acuity was better than 20/200, that the device go into the poorer seeing eye, and if it were otherwise, then it was a physician/patient option after discussion.

Regarding lessons learned, in terms of looking at the clinical data, I believe not in all cases but in most cases, we recommend looking at the results using the external telescopes during preoperative assessment to understand the achievement we would expect after implant of the IMT to see if the gains were sufficient. We would like to see two lines or better, better than the fellow eye. If that's achieved, then I think putting it in the poorer seeing eye is fine.

However, we would like to see significant improvement over whatever the fellow eye is. In general, I think we would recommend, just looking at this, that the device go into the better seeing eye in most situations. We also find it's slight, and

maybe -- it could be noise, but we see the retention of gains in visual acuity when the device went into the better seeing eyes, somewhat better out over time. Adaptation.

DR. PELI: Before that adaptation, I think it's crucial that after surgery, the implanted eye has better acuity than the patient had before. If we don't achieve that, then we miss the point, and in some of the cases in the study, that was the outcome, but it was imposed by that protocol. So we would not recommend that as a practice going forward.

The patients that had that situation ended up not having a lot of incentive to use that eye if they had better acuity in the other eye and better field, you know. So they didn't adapt well. The adaptations are surprisingly varied. So there's no fusion. Nobody's fusing with the 3X or 2.2X difference. The patients are switching. They're alternating, and they develop a variety of methodologies to do it on their own. Some blink and switch over with a blink. Others are just trying, that they can -- and we are now trying to help some of them in training by putting a partial tape on the lens to enable them to switch from one eye to the other. We're thinking of that as a method of

training and/or as a matter of continuing use.

MR. HILL: Just a quick elaboration on that. On the lessons that we've learned regarding this particular topic, we've incorporated this into the training programs that have been submitted to the Food and Drug Administration for (a) preoperative assessment, (b) postoperative -- I don't think I would call it rehabilitation, but I would call it vision training for learning how to learn to use the new vision status. Thank you.

DR. WEISS: Richard and then Janet.

MR. BUNNER: Just a general question on the patient brochure, on pages 9 and 13, there's reference to contraindication of patient rubbing their eyes, and I notice that there was no adverse effects related to that postoperatively, but is there any greater risk with eye rubbing as a contraindication than there would be with IOLs?

MR. HILL: The answer is there is significant risk for a chronic eye rubber, and we should call that out. If it's not clear in the labeling, we should do that because this device protrudes very slightly through the plane of the iris. So an individual who particularly vigorously rubs their eye, there is potential for the device and

cornea to come in contact. I must say, we don't have any specific evidence of that occurring, but it is a potential risk, and I would advise any surgeon to not implant a chronic eye rubber.

Same thing would apply for someone, there are a few individuals who sleep on their face and sleep on the one eyes. That could be a risk also. So those subtle things should be avoided, but in general, avoid eye rubbing.

MR. BUNNER: None of the 217 patients, there was no adverse events related to eye rubbing?

MR. HILL: I can't say with any authority because none of us were there. So we can't say.

DR. WEISS: Janet.

DR. SZLYK: I just have two questions. One relates to the quality of life data. I realize that the primary effectiveness measure was visual acuity. I was wondering if there was any information that you could provide on the variance of the quality of life data that were presented by Dr. Stulting for the improvements and if that may impact our interpretation of these data in any way?

MR. HILL: We previously submitted to FDA submissions, there was -- I think this would be in regard to relationship between visual acuity and

improvement in quality of life. In terms of other factors, I can't necessarily elaborate, but as it relates to improvement in visual acuity, those subjects who gained two lines or more in both distance and vision had a statistically significant and clinically meaningful improvement in quality of life as compared to those who did not.

Is there a lesson there that possibly we can look at? I think with utilization of the external telescopes, we do look at both distance and near. We did not consider that factor, of course, before doing the trial but, you know, I think the improvement was approximately on the composite score of about seven points, in the VFQ, for those with both, two lines of both, versus those that didn't. Is that --

DR. SZLYK: That answers my question.

MR. HILL: Okay. Thank you.

DR. SZLYK: So it was for that subgroup that you found.

DR. WEISS: Did you have a follow-up question?

DR. SZLYK: Yes.

DR. WEISS: That's fine.

DR. SZLYK: A second question. Dr. Schein

talked about the low vision strategies that were employed prior to enrollment in the study and the decision whether to have the implantation. I was just wondering if eccentric viewing was also considered in that low vision rehabilitation before, prior to surgery, given that we're seeing the effect of the Stargardt patients who have a lifelong adaptation to eccentric viewing, that this may be employed for all patients.

MR. HILL: If you wouldn't mind, would you summarize your question or your statement again, please?

DR. SZLYK: So my question was you had a low vision rehabilitation specialist working up the patients ahead of time. Was there any eccentric viewing training that was done?

MR. HILL: Eccentric viewing is discussed as a formal part of the training program. It is more pronounced in the revised training program that we're recommending, assuming we're approved. So the answer is yes.

DR. SZLYK: Thank you.

DR. SUNNESS: I have a related question.

DR. WEISS: Yes.

DR. SUNNESS: Did you find if people had to

go more eccentric, and this is sometimes the case in Stargardt's patients, was it harder for them to use the telescope?

MR. HILL: I'm going to defer to Dr. Peli on that. I don't believe we have any data on that, Dr. Sunness, I'm sorry, but Dr. Peli.

DR. PELI: There was no data collected with imaging as low or night or anything of that sort or even visual field that could have possibly get, but the field of the telescope on the retina, even for the 3X model, is in the range of 50 degrees. So the scotoma, the lesion, is what, large is 10 degrees. We're talking about a small fraction of that field, and there's no field interference. So I think this is not playing the role except in the case where it's completely -- or something like that.

DR. WEISS: We're going to have Eve, David, then Frederick, and then most likely end this question session subsequently and then have a 10-minute break. So I'm just going to give you a little bit of what's to come. Eve.

DR. HIGGINBOTHAM: I have three questions. I think two of them are rather quick. On page 88 of the executive summary, it's noted that 18 percent of the patients had pigment inflammatory deposits. It's

certainly expected that there will be some inflammation. What was not noted, however, was whether or not there was any visualization of the angle. My concern is if you have significant inflammation early on, if there is some zipping of the angle that can occur over time, that may not actually demonstrate any clinical evidence of an issue until years down the line. So if you could comment on the gonioscopic appearance of these patients in this long-term study.

MR. HILL: If I may answer the questions in reverse order. Regarding the gonioscopy, we have measures on approximately 40 patients. I do not believe they're in here. The angles were wide open in all but one patient. That patient in particular had a tilted IMT, one loop was in the sulcus, one was in the bag. Dr. Stulting on chronic inflammation.

DR. STULTING: The cylinder of the IMT protrudes through the pupil very slightly, and so when these patients constrict their pupils postoperatively, the iris comes into contact with the cylinder, and I think that's the mechanism for the inflammatory and pigmentary deposits that we saw on a few of these eyes. We treated some of them with steroids when they developed the inflammatory

deposits usually a few months after the implantation, and they all went away. I think the iris habitually, I think that you get an adaptation so that the iris no longer bangs up against the cylinder, and we had no one who had chronic inflammation as a result.

DR. HIGGINBOTHAM: I guess my question was not so much the mechanism of the inflammation but what was the appearance of the end goal among those patients that had significant inflammation early on? There were about 51 eyes.

DR. STULTING: In my population, there was no discernible difference, and I'll turn the floor over to Steve Lane and Mr. Hill to address it further.

DR. LANE: I think the ideology obviously, as Doyle pointed out, in the large incision and the greater amount of surgery for the inflammation, but it was an acute inflammatory process due to the surgery that cleared with steroids, and actually just to amplify on Doyle's statement just a little bit, the amount of pigment was fairly minimal. It's the amount that was sort of collected as it banged up. It was mainly seen at the base of the cylinder anteriorly. So when we did gonioscopy on these patients, it was very little pigment in the angle to

be cleared. It wasn't sort of a huge influx of major pigmentary loss. It was a small amount of pigment that was noted. And, in fact, we actually modified the protocol following the first few implantations to chronically dilate the patient for the first month or so after surgery so that you avoided that hippus effect against the cylinder, and that basically significantly reduced the amount of inflammation. But I think to answer your question, the amount of inflammatory debris seen in the angle, the amount of pigment seen in the angle was minimal.

DR. WEISS: Thank you. David.

DR. HIGGINBOTHAM: I wasn't -- well --

DR. WEISS: Eve, if you had a follow-up, that's fine.

DR. HIGGINBOTHAM: Well, yeah. Well, I have a follow-up, and I had a couple of other questions. But it does appear in the 50 patients that have the significant inflammation, that gonioscopy was done on a formal basis to actually determine if there were any peripheral anterior sneaky eye, not just pigment scattered in the angle.

MR. HILL: Allen Hill. I don't believe we will be able to answer that question. The gonioscopy was done later in the study at the request of FDA.

So that population of approximately 40 patients was done at approximately 36 months postop.

DR. WEISS: So we don't know how many of those patients intercepted the 50 that had high pressure versus the 40 that had gonioscopy afterwards?

MR. HILL: We have not done that analysis, no.

DR. WEISS: Okay. So we don't have that information.

DR. HIGGINBOTHAM: I had two quick questions. The 50 percent of the Stargardt's patients that were explanted, given that high number, is it possible to tease out some additional patient selection criteria that would help guide future surgeons?

MR. HILL: That's a good point. We are not recommending or not recommending that Stargardt's patients be selected for implant at this time.

DR. HIGGINBOTHAM: Okay. And then just one final question, Madam Chair. The number of cells that one can lose and still maintain clarity, I recognize, is not something that anyone can predict, but as a glaucoma specialist, I'd like to get some reassurance that if you go as low as 750 which, of

course, is certainly far out on Dr. Schein's risk model, but even when you think about 15 years out, and losing as many as 50 percent of your cells, that seems like a lot of cells that one can actually achieve in this model that's presented here.

I guess if either Dr. Edelhauser, who I know is here as well as the cornea specialist, can just reassure this glaucoma specialist that losing 50 percent of one's cells is still compatible with a clear cornea and not necessarily would suggest that all these patients will go to corneal transplant.

DR. STULTING: Doyle Stulting. I think the literature and common experience and common knowledge will tell us that 300 to 500 endothelial cells per millimeter squared is the threshold for the onset of corneal edema, rather than the percent of cells that are lost. In fact, the estimates that the company has made with regard to initial cell counts are ones that I personally have argued against because I thought that they were much too conservative, and they're much too conservative in a couple of ways.

First, the mathematical model looking at chronic endothelial cell loss predicts a greater cell loss than was actually observed in this population or any of the reported populations using traditional

surgical techniques which are essentially the same. So it's conservative in that way. We chose a cutoff of 750 cells per millimeter squared, which is conservative as well.

This is an elderly population of patients who are very likely to outlive corneal edema if it occurs.

The other way that we are very conservative is that the onset of corneal edema in a person who has potential 20/20 retinal acuity can be problematic when the corneal thickness increases very slightly. But remember, these are patients who are significantly visually impaired. So they have to get more than just a little bit of corneal edema for it to be a vision limiting factor.

So for those and other reasons, I think that the grid that was created is much more conservative than we really need to have as a guideline.

DR. HIGGINBOTHAM: Thank you.

DR. WEISS: Actually, Doyle, if you could stay up there for a moment, and I may need Hank to also answer this one. The minimal ECD grid that was presented with females of 65 to 69 requiring 3200 cells and males 2800 cells, what is the typical --

that's not in my population. So what's the typical patient in that age category have, and with those criteria, would you be able to enroll any patients?

DR. STULTING: That's part of the reason that I am a little bit considered about the layers of conservatism that went into these calculations. They compound themselves because we're selecting an endothelial cell density for the endpoint that is higher than what we know brings on corneal edema. We're selecting a rate of decompensation that is higher than what we measured. We're going to the 90 percent confidence interval, which adds more conservative padding, and we're looking at all comers rather than those that are implanted by trained surgeons.

So for a number of reasons, these numbers are very, very conservative, and I do have some concern about whether that might exclude some people who would like to have the implant, knowing the risk and knowing that they may face the issue of visually significant corneal edema down the road.

We still may be able to give these people who have 10 years perhaps of life expectancy another five or six years of very good benefit from the IMT before a problem arises, and it's a good point.

DR. WEISS: Just to clarify though for the Panel, do you have -- I'm sure, Hank, you probably have numbers, in age 65 or 65 to 69, what would average endothelial cell count be?

MR. HILL: The average ECD for the patient population on entry was 2500 cells per millimeter squared. As you would expect, on the younger, in the trial, we enrolled patients down to age 55. As you would expect, they had somewhat higher ECDs and then it diminished with time. It's not in this submission, but it was stratified in the information that we provided to FDA in the original submission. They are, however, modest differences as you go out over time.

DR. WEISS: Okay. So practically, just dealing with a real life situation, if we were going to use the minimal ECD grid as a guidance, we wouldn't be able to enroll most likely anyone less than 70 because they wouldn't have -- you wouldn't be finding people with that number of cells. So either you have to restrict yourself to the older age categories, 70 or above, and I don't know if those people still, if you increase the age, would have as many endothelial cell counts as you'd need, or you'd be forced to specify we need, do you have a corneal

surgeon, no guttata or ACD of 3 or more. Is my understanding correct?

MR. HILL: That's correct. I think the issue before the Panel today regarding the grid that is preferred and recommended by the Panel will be addressing that exact issue. If we take all IMT-implanted eyes or IMT-implanted eyes in a grid developed from that, you are correct. There will be very limited patients that would meet that criteria. On the other hand, as presented and discussed by Dr. Schein, if there is a recommendation to select the grid that's based on not the full risk reduction but the partial risk reduction of non-guttata eyes, ACD greater than 3, then there is a reasonable likelihood that we would get at least, I would estimate, approximately 50 percent of the population in that age group that would be candidate patients.

DR. WEISS: Thank you very much. David.

DR. MUSCH: I have two questions/comments. The first is with my epidemiology hat on, and this is directed to Dr. Schein who is not only an excellent anterior segment surgeon, but I know he's an epidemiologist, too, and that relates to risk-reduction strategies that were employed. If you, like we Panel members, read the executive summary,

you will see that (a) the post hoc testing that was employed, I understand was mostly driven by either questions from the FDA or questions from the previous Panel. And so you were beholden to do many of those post hoc tests. I understand that, but yet you are being held to a standard that there is bias introduced by post hoc testing, and you might be criticized for relying upon multiple testing and not adjusting your p-values for that.

Now I didn't see many p-values in your report, but tell me, did you make your risk-reduction strategy judgments based on p-values or based on biological and clinical plausibility?

DR. SCHEIN: Well, I think, as you know, the biggest issue with post hoc analysis comes up in randomized clinical trials, you know, comparing, for example, drug A to drug B. You do the overall comparisons that were intended, announced beforehand. You find no effect, and then you start searching for subgroups in which, in effect, in the same comparisons A to B come out. And then if you draw inferences from that, you've gone down this slippery slope.

I think this is a very different situation here in that we have a case series with endpoints

that were established on a full cohort, and I think the safety and efficacy data stand on the full cohort. And then there's some obvious commonsense clinical factors that one can look at, but these are, you know, looking at guttata as a risk factor for corneal edema is self-evident. Anterior chamber depth, I believe, is equally self-evident. The corneal training is not built into the grid, but there is a clear effect and, in fact, that was probably the strongest of the three effects that were found, and there's something there, whether it's, you know, an innate respect for the cornea or it's dealing with large wounds or, you know, the gray hair and the large experience with extracaps earlier in life. Something is there, and they're biologically or surgically based on plausibility, not statistical analyses.

So when one applies these at the end, it's with an attempt to make the introduction of the device into the population that will receive it more safe. It's not -- the only place where there's a potential post hoc analysis is in the derivation of a grid, and every piece of the grid, of any grid that anyone chooses is based on assumptions. Each one of those assumptions can be held to higher or lower

specificity thresholds.

DR. MUSCH: Thank you. And my second question relates to the decision to include subjects who had an initial vision of 20/80 to 20/160. There are sections in the report where you refer to a patient with 20/100 vision as being quite functional in daily life activities, recognizing forms and things like that. I wondered why you set that threshold so low, and perhaps you could give me an example of a patient who presents with 20/80 vision and yet would be a candidate for the IMT. And I want to add that there were only 15 patients that fell within that category.

MR. HILL: I'm better quoting the statistics and the data than I am regarding necessarily patient selection, but let me address some of the numbers.

In that group that were 20/160 or better, in terms of achieving the visual acuity endpoint, they were met. I think it's approximately 80 percent of that small group that achieved two lines or better. In terms of why, to go back to why did we select that, that was on the advice and counsel of a number of advisors that participated in the development of our clinical trial in concert with

discussions with the Food and Drug Administration. The level of 20/80 is pretty well recognized with WHO and other organizations as being the onset of a sign of visual impairment, and that was one of the primary driving factors.

We also looked at what were, and we didn't know at the time, what were the theoretical improvements that we could see in visual acuity with this patient group. Dr. Peli has been an advisor to us for a long period of time. We have known for that long period of time that subjects that have better visual acuity will not yield the full benefit of a telescope as compared to individuals that have severe vision impairment. However, there's still good potential to gain significant vision, which I think was borne out by the trial. All I can say is the data stands on its own in regard to the achievement of visual acuity and did that group, for instance, gain -- did that percentage gain, let's say the percent gained in three lines, was it as significant? The answer is no. But did they gain two lines? Yes.

So we're in that fine area between what is significant. I think the literature is varied on that issue, whether two lines or three lines is significant, but I think both are meaningful, and I

can understand what Dr. Peli says, more vision is better vision in this patient group.

DR. MUSCH: It's been instructive, too, to provide us with mean visual acuity for those various strata of baseline visual acuity.

MR. HILL: We can do that.

DR. MUSCH: Okay.

DR. PELI: Eli Peli. If I can just add a little to that. So what happened is that patients that have worse acuity gain more in terms of acuity with a telescope, but if you think about what patients do with acuity, then as they lose what they can do, is shrinking, so if you take yourself on a lower place on that pyramid, then they can get to do more. So actually when I have a patient walking in, and I open the chart and it shows something in the range of 20/80 to 20/100, I'm good. This is going to be a good session. Everybody's going to be happy. And so that's not any different with a telescope. It's going to give them more functionality in terms of the number of things they can do and improve with.

DR. WEISS: Thank you. We're going to have Frederick, and then Alice, and I would like to make the questions briefer now and the answers briefer as well.

DR. FERRIS: I don't know how brief I can be. I'd like to start by saying that I think people ought to be given choices and that this sponsor has done a pretty nice job at least to me to show that some people clearly benefit from this device, and I think we heard from some people who clearly benefited, and we didn't even hear from the cats.

So some people benefit. Our job, unfortunately, is that we're left with balancing the benefits with the risks, and that's where I start having a hard time. As Oliver said, this is a case series basically, and you have to use historical controls or other controls. I think some of the data that we were given, are we to compare this intraocular telescope with just an intraocular lens, or do we compare it with an intraocular lens plus an external telescope? And I agree completely with Eli that if you could have an internal telescope, that would be better, but some of the data I think, for example, it seems a little ingenuous to me to say, well, more of the intraocular lens patients lost vision than the telescope patients because, and if I'm wrong, I'd like to be corrected, those weren't intraocular lens acuities plus a telescope. Those were just the intraocular lens acuities.

So, of course, I presume it's against baseline visual acuity without a telescope. So, of course, if you have telescope, you're more likely to not lose vision. So it's not exactly apples to apples, and I just want to make sure that I'm correct about that. I'm not sure that it makes a huge difference in the way I look at this, but I think if we have not learned anything from the LASIK experiments where most people do very well, but some people, and there's a website I guess, lasiksucksforyou.com. There's some people who are very upset, and I think they're upset mostly because they didn't understand in advance what their risks were. So it seems to me that our job is to make sure we can tell people what their excess risk is, and maybe Oliver can help me out. I'm not sure if anybody can really tell me what I'd love to know, and that is if I have cataract surgery, I have a risk of developing corneal edema. If I have cataract surgery, I have a risk of developing a retinal detachment. Those don't go away with this procedure, and they may be enhanced somewhat, and it's the somewhat that I don't know. Are you at double the risk or are you triple the risk?

And I think it would be important to be

able to tell patients that you have this benefit but you're going to double your risk of developing corneal edema, and I don't know what the denominator to the seven patients that have corneal edema is. It's a little hard to know what that percent is, and it's hard for me to know, well, if I had a comparable group, these are pretty old patients, how many of them would have developed corneal edema if they just had cataract surgery.

So I don't know what the relative risk is. I don't know what the relative risk, if and when. Some of these people are surely going to develop retinal detachment. Their excess risk for retinal detachment based on cataract surgery doesn't -- I assume the devices doesn't protect them from that. So they may have some excess risk with regard to the success of their retinal detachment surgery, both noticing the detachment early on as well as repairing it because of maybe somewhat difficult observation during surgery.

So I wonder, for me, it would be important for the sponsor to try to give us estimates of these risks that we can tell our patients, here's the benefits that you can get but make sure you understand that there's no free lunch and here's your

excess risks.

DR. WEISS: Yeah.

MR. HILL: Allen Hill, Dr. Ferris. We agree. We should fully inform the patient of the risk. In our proposed labeling, very similar to what Dr. Schein discussed in his clinical perspective, we intend to include explicit risks and strongly recommend that there be a discreet physician/patient conversation regarding the risk of this device. The risk of corneal edema is, from my perspective, higher than what you would find in the normal population of elderly that are undergoing conventional cataract surgery. The information presented on lines lost were in fellow eyes, that was really a safety measure. I won't add to that, but I believe you are fully correct, and we should be very explicit about risk.

DR. FERRIS: I'd like to just make one last comment. I know you want to get me off this, but I agree with something that Doyle said, and that is Oliver put together a nice grid, and it says if you fit within this grid, your chances of having corneal edema are dramatically reduced. On the other hand, I can imagine a patient who has good, very good reason for one of these implants who has a somewhat lower

endothelial cell count, and it seems to me that as long as Doyle tells them, look, we can do this, you're going to be at somewhat extra risk, here's some of the things we're going to do to prevent that from happening, and make sure you document that the patient understands that. There's nothing that I know of that would prevent him from going ahead and implanting this device.

DR. WEISS: Alice.

DR. MATOBA: I agree with all those comments, and also I think that in patients who do have a significant visual loss from macular edema, the effect of the corneal edema on their visual quality may not be as great as someone who started out with 20/20 immediately after cataract surgery. So that should also be taken into account, and although the risks are there, it may not be as great in terms of impact on a patient as it would be in a normal patient.

And along the same lines, I'd like to say that these risk reduction strategies that Oliver put together, the second one, 65 years or older, it almost seems to imply that if you're under 65, you're not a good candidate for this implant, and yet that's the age group where you're most active and you may

have the most to gain from better vision, and somehow this one thing is different from the others in that the risk benefit -- all the others like AC depth of greater than 3, it's just purely risk, but this is risk benefit, and I wonder if you might rethink it or reword it or do something different about that age group because you haven't clearly shown that -- well, anyway, I'll stop right there.

DR. FERRIS: Some of us don't view 65 as old. I don't.

DR. MATOBA: No, not at all.

MR. HILL: Dr. Matoba, Allen Hill. We did include or enroll patients 55 and older in the trial. There were just a few. We would welcome the Panel's recommendations on how we would approach that.

DR. WEISS: We're going to close this session, and there will be an opportunity for questions later on as well, as well as the sponsor following up some of the questions that were asked here.

We're going to have a 10-minute break, and then we're going to come back to the room for the FDA presentation.

(Off the record.)

(On the record.)

DR. WEISS: I call this meeting back to order. We are now going to hear the FDA presentation. Malvina wants 60 more seconds.

DR. EYDELMAN: I have to account for people's caffeine intake in the morning.

DR. WEISS: Now we can start. I forgot we need the presenter. Details, details. So now I would actually like to call the meeting back to order.

We're going to start with the FDA presentation, and the first FDA presenter is Don Calogero, the review team leader for this PMA.

MR. CALOGERO: Thank you. Hi, there. I'm Don Calogero, team leader for this PMA for the IMT.

Briefly, I want to go over the regulatory history. At the IDE phase, the original IDE application was approved to begin the clinical study May 2000. In October 2002, the IMT-002 protocol was approved, and then in February 2006, the long-term monitoring protocol was approved.

The PMA was submitted in 2005 in multiple phases as you can see this, from 0 to 4, and module 4 was the clinical data which converted to a PMA.

On July 14, 2006, this PMA was taken to the Ophthalmic Panel meeting, and on a 10 to 3 vote, they

voted not approvable due to safety and effectiveness concerns with the device.

After that Panel meeting in 2006, the sponsor subsequently submitted amendments 6 to 19 to address outstanding issues with their device.

I want to thank the FDA review team. As you can see, it's fairly extensive. I won't review all of their names, but this was our FDA review team.

The FDA presentation today consists of four parts. Dr. Lepri will go over the general clinical summary. Gene Hilmantel will go over the specular microscopy summary. Yao Huang will go over the statistical summary, and Michelle Bonhomme will talk about postmarket approval summary.

So now Dr. Lepri will talk about the general clinical issues.

DR. LEPRI: Good morning, distinguished members of the Panel, VisionCare Technologies, FDA colleagues and guests.

This morning I will present to the Panel a brief summary of the sponsor's responses to recommendations from the July 2006 Panel meeting along with other clinical issues.

The IMT study population has evolved over time. Two protocols were instituted. The original

protocol was IMT-002 where 218 subjects were enrolled. Of these, 206 were successfully implanted; 129 subjects who participated in and completed 24 months follow-up of the original PMA clinical trial were asked to voluntarily participate in protocol IMT-002-LTM, the long-term monitoring study.

This chart provides the accountability of the IMT-002 protocol. Throughout the PMA clinical trial, accountability was excellent. At 12 months, accountability was reported at 97.5 percent and, at 24 months, 92.6 percent highlighted in the bottom row.

Here we have a tabulation of the accountability of the long-term monitoring study that was conducted by the sponsor. 129 subjects who participated in and completed 24 months follow-up of the original PMA clinical trial were asked to voluntarily participate in the long-term monitoring study. Only three subjects were available at 30 months due to the time involved in the re-enrollment process, but then you can see it progresses rapidly. At 48 months postop, accountability is 86 percent.

Since submission of the original PMA, the sponsor has modified their statement of indications along with the addition of contraindications and

warnings resulting from in-depth analyses of the ongoing data. These modifications include age, anterior chamber depth, integrity of the corneal endothelium at enrollment, as well as other factors. The Panel will be asked to provide recommendations on this proposed patient population.

The statement of indications under consideration by the Panel reads as follows:

The Implantable Miniature Telescope is indicated to improve vision by monocular implantation in patients 65 years of age or older with stable moderate (distance BCVA of 20/80 or poorer) to profound (distance BCVA of 20/800 or better) vision impairment caused by bilateral central scotomas associated with end-stage age-related macular degeneration. Subjects selected for implantation should meet the following criteria: retinal findings of geographic atrophy or disciform scar with foveal involvement as determined by fluorescein angiography; evidence of cataract; at least a five-letter improvement of the Early Treatment Diabetic Retinopathy Study Chart with an external telescope; adequate peripheral vision in the eye not scheduled for surgery; and willingness to participate in a postoperative visual training/rehabilitation program.

In addition to the modifications to the statement of indications, the sponsor has proposed several new contraindications which further define the patient population.

This slide summarizes the differences in the proposed population between the 2006 and the 2009 Panel meetings. In 2006, the minimum age was 55. In 2009, the minimum age is 65.

The originally proposed patient population was for patients who had stable central vision disorders resulting from AMD determined by fluorescein angiography. This was changed to stable, moderate to profound central vision impairment, for example, distance BCA of 20/80 or poorer to 20/800 or better, due to bilateral central scotomas associated with end-stage macular degeneration defined as retinal findings of geographic atrophy or disciform scar with foveal involvement as determined by fluorescein angiography. And originally, IMT patients were to show interest in participating in a vision rehabilitation program, and now they must be willing to participate in one.

Continuing on, a contraindication for patients for corneal guttata has been added to the definition of the patient population because it was

identified that these patients are higher risk for ECD loss. Originally, there were no contraindications for a specific anterior chamber depth. The anterior chamber depth was specified in the inclusion criteria but not contraindicated in the labeling. The sponsor has added a contraindication restricting anterior chamber depths of less than 3 millimeters.

The original IMT protocol contraindicated subjects with an ECD of less than 1600 cells per millimeter squared. Because postoperative ECD loss over the life span is a significant clinical entity, the sponsor has now proposed a minimum baseline ECD grid based upon age of entry and proposed life expectancy that they believe will enhance the safety profile of the IMT.

Effectiveness. The effectiveness endpoints of the IMT trial reported changes in visual acuity by lines gained or lost. FDA requested that the acuity outcomes be presented by the actual mean visual acuity achieved by 24 months. The mean best-corrected distance visual acuity at baseline was 20/312. By 12 months postop, it had improved to 20/141, and by 24 months, it was 20/149 as measured on an ETDRS acuity chart.

Near acuities were also reported in this study, and the mean best-corrected near visual acuity at 16 inches was 20/262 at baseline. At 12 months postop, it had improved to 20/149, and at 24 months, 20/157.

In this study of population, it was also important to analyze the change in degree of visual impairment. Over 75 percent of subjects in the clinical trial improved their degree of visual impairment; 72 percent of subjects categorized as having severe or profound visual impairment in this study achieved postoperative visual acuities at one year ranging from 20/80 to 20/160. At two years postop, 70 percent of those with severe or profound visual impairment achieved an acuity ranging from 20/80 to 20/160.

The improvement in visual acuity and degree of visual impairment combined provide a clearer picture of the potential overall effectiveness of the IMT.

The sponsor was asked to stratify visual acuity outcomes based on whether the implanted eye was the subject's better or worse eye. For all IMT-implanted eyes and a 24-month consistent cohort, the difference in visual acuity between IMT-implanted

eyes that were worse versus those that were better or the same at baseline persisted through the course of this study. The different was largest at baseline and smaller at follow-up visits, with relatively small between-group differences observed. The analysis revealed that there were no major differences, only small ones.

Corneal adverse events and specifically transplants have undergone in-depth analyses. The following tables present the tabulation of explants and corneal transplants up to and beyond the 24-month follow-up period. In other words, they include events from both protocols IMT-002 and IMT-002-LTM, the long-term monitoring study.

The Panel will be asked to provide recommendations on these analyses with respect to the safety of the IMT.

Eleven subjects were not successfully implanted. Five implantations were aborted at the time of surgery due to unrelated surgical complications. Six IMTs were removed intraoperatively. Eight IMTs were removed postoperatively within the first 24 months of the study, for a total of 14 removals within the first 24 months.

There were four additional explants that occurred after the 24-month time interval, bringing the total of postoperative explants to 12, which is 5.3 percent of the operated implanted population. Of these 12 subjects that had the device removed, 2 were due to device failures regarding cracked housing and condensation, 8 explants were due to dissatisfaction, and 2 cases were due to corneal decompensation. Subsequently, the total number of IMT removals, intraoperative plus postoperative, for all time periods was 18 or 8.3 percent of the population.

Overall, evaluation of the endothelium reveals that at the final visit for each patient, there were about 9 eyes with unresolved corneal edema, 4 resulted in decompensation with transplant, 2 decompensations occurred without transplant, and there are apparently 3 additional cases of ongoing corneal edema.

The analyses further show that there are 19 eyes or 9.2 percent of the original PMA cohort of 206 implanted eyes that had ECDs less than 750 at the last reported visit, and there are 31 or 15 percent of eyes with ECDs less than 1,000.

The Panel will be asked to address the safety and effectiveness in the following question:

The Implantable Miniature Telescope is indicated to improve vision by monocular implantation in patients 65 years of age or older with stable moderate (distance BCVA of 20/80 or poorer) to profound vision impairment (distance BCVA 20/800 or better) caused by bilateral central scotomas associated with end-stage age-related macular degeneration. The patients must meet the following criteria: retinal findings of geographic atrophy or disciform scar with foveal involvement, as determined by fluorescein angiography; evidence of cataract; at least a five-letter improvement of the ETDRS chart with an external telescope; adequate peripheral vision in the eye not scheduled for surgery; as well as a willingness to participate in a postoperative visual training/rehabilitation program.

The contraindications under consideration are evidence of corneal guttata; anterior chamber depth of less than three millimeters; the IMT is contraindicated in patients who do not meet the minimum age and endothelial cell density as specified in the proposed grid; additional contraindications as proposed by the sponsor in the labeling.

Please discuss whether the sponsor has provided reasonable assurance of safety and

effectiveness of the device for the proposed indications and contraindications. What, if any, modifications to the proposed patient population do you recommend?

The presence of the IMT in the anterior chamber raised the question at the last Panel meeting of ease of visibility of the fundus. The sponsor provided an analysis of over 1800 fundus examinations performed with a variety of techniques. For all of these techniques, good dilation was a key factor in successful performance, especially for binocular indirect ophthalmoscopy and the use of the 90 diopter handheld lens in conjunction with the slit lamp.

The techniques reported on were diagnostic photography; optical coherence tomography and/or B scan ultrasonography; slit lamp with a 90 diopter handheld lens; fluorescein angiography; and indirect ophthalmoscopy, 50 to 60 degrees of retina visible when fully dilated and limited visibility when full dilation was not possible.

The Panel will be asked to provide recommendations on the evidence provided to support visibility of the fundus with the IMT-implanted patients.

In the analysis, investigators were asked

to rate the effectiveness of the examination techniques they performed. Of the 1,821 fundus examinations performed, only 9 exams were reported to have had uncertain effectiveness. This translates to a rate of 0.5 percent. The failure rate using the 90 diopter lens for fundus examinations was reported to be 4 percent. Direct visualization with contact or non-contact viewing lens was rated as the best and most effective way to evaluate the fundus.

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.

The sponsor was also requested to analyze the effect of cataract removal and IOL implant alone in comparison to IMT-implanted eyes for change in visual acuity. Twenty-two fellow eyes of IMT subjects had cataract removal with IOL implants. Their mean improvement in visual acuity was .35 lines as compared to the mean improvement in IMT-implanted eyes which was 3.43 lines.

This slide presents the graphic comparison of the visual acuity improvement in IMT-implanted

eyes compared to the theoretical gain and gain in acuity resulting from cataract removal and IOL implantation. Clearly one can see that the improvement in visual acuity attributed to the IMT is significantly greater than that achieved by cataract extraction and IOL implantation alone. So the apparent contribution of cataract removal to visual acuity improvement was minimal for this population.

This next graph shows the actual gain in lines of best-corrected distance visual acuity at baseline, with an external telescope, as compared to the theoretical gain from the external telescope, taking into account the gain attributed to cataract removal. Patients with severe to profound visual impairment due to end-stage macular degeneration did not achieve the theoretical gains and visual acuity when visual acuity was assessed using a wide field external telescope.

The Panel will be asked to provide recommendations on the effect of cataract removal and IOL implantation alone as compared to the change in visual acuity attributed to the IMT in the following question. Has the sponsor adequately demonstrated the effectiveness of the IMT, taking into account the analyses of visual acuity improvement in eyes with

cataract removal without IMT implantation?

Thank you.

DR. HILMANTEL: Hi. I'm Gene Hilmantel, and I'm going to speak about the specular microscopy results.

Before we get started, I have some information on one of the Panel questions that was asked. We were able to get some data on seven eyes that had the IMT explanted during the study. Five of the seven either showed virtually no loss or showed a gain in cell counts. One eye lost 250 cells per square millimeter, and one eye lost 1200 cells per square millimeter approximately.

I also want to clarify something about the study design. A few people have referred to the fellow eyes as a control group. The protocol did not call for a control group in this study. Later FDA did request some comparisons to the fellow eyes for some of the ECD outcomes and for some of the acuity outcomes. This has some utility, but these analyses should be interpreted with caution. For example, there were no exclusion criteria for minimum baseline ECD for fellow eyes while IMT eyes had an exclusion for ECDs less than 1600. Additionally, the pseudophakic fellow eyes comprise quite a mix. Many

of these had IOLs implanted before enrollment, possibly many years before enrollment. Twenty-two eyes had IOLs implanted, fellow eyes I'm talking about, had IOLs implanted during the study at varying time points in the study.

Okay. In my discussion today, I'll provide a brief background followed by summaries of study results concerning acute and chronic loss in endothelial cell density, morphometric analysis, the risk of corneal decompensation and late corneal edema, and the risk of eyes ending study at low levels of endothelial cell density.

At the 2006 Panel meeting, endothelial cell density data from preop to two years postop was presented. The Panel expressed concerns about the ECD decline presented. The Panel and subsequently FDA recommended analyses of morphometric data in order to help characterize endothelial changes, analysis of longer-term follow-up data to estimate the acute and chronic rates of ECD loss, and analysis to further identify cofactors that might be used to help mitigate the risk of decreased ECD.

The sponsor has analyzed the effect of cofactors in an attempt to mitigate the risk of loss. They have performed multiple post hoc tests for the

significance of several cofactors, including the anterior chamber depth, surgical specialty, surgical order, glaucoma, chronic inflammation, diabetes, and guttata.

The sponsor has suggested that the following are risk factors for endothelial cell loss: baseline presence of corneal guttata, baseline anterior chamber depth less than 3 millimeters, implantation by a non-cornea-trained surgeon, being among the first five eyes implanted by a given surgeon.

As shown in the slide, the first two of these factors have been incorporated into contraindications, the third has been incorporated into a warning, because of the fourth factor the sponsor is requiring a special training program for surgeons. Additionally, baseline ECD has been shown to have some relationship to low postop ECD. Minimum baseline ECD is now part of a proposed contraindication.

The sponsor has presented results from various subgroups. The all IMT-implanted cohort consists of eyes that have had surgery and had the IMT-implanted and not removed intraoperatively. The guttata-free large ACD sub-cohort is a subset of the

above that only contained eyes with no guttata and anterior chamber depth greater than or equal to 3 millimeters at baseline. It is similar to the indicated population but without the age restriction limiting patients to age greater than 65 and without the minimum baseline ECD contraindication.

Sub-cohort A is a subset of this prior group. It only contained patients that had no guttata and ACD greater than or equal to 3 millimeters at baseline and patients greater than or equal to 65 years of age and implanted by a cornea specialty. Sub-cohort A represents approximately the indicated population plus a restriction concerning surgical specialty contained in a warning.

The sponsor also refers to sub-cohort A as the fully risk reduced cohort. The sponsor has provided the key outcomes for each of these three groups of eyes.

This table provides the number of eyes with available ECD data for these cohorts. The portion in black shows the numbers available in the initial IMT-002 phase of the study, and the portion in red shows the numbers available for the LTM or long-term monitoring phase of the study. The shaded portion in red shows the number of patients that reenrolled into the LTM portion of the study for each sub-cohort.

As you can see, at least 80 to 85 percent of the implanted eyes were available at each visit through 24 months postop. The numbers available for follow-up dropped dramatically after 24 months. All of these post-24-month visits had fewer than half of the number of eyes seen at preop. So keep in mind that the results for this time period have to be interpreted with caution.

I do want to point out that in that sub-cohort A in the LTM phase, most patients came from only one or two sites as there were very small numbers of patients available.

As you're all well aware, the endothelium is the layer of the cornea that pumps water out of the cornea keeping it from getting edematous. A decline in ECD to low levels, say 500 to 1,000 cells per square millimeter, puts the eye at risk for corneal decompensation, severe edema causing corneal opacification. Just as a point of reference, from mod and small incision cataract surgery, the mean acute or surgery-related decline is approximately 5 to 8 percent in the first several months following surgery.

The safety endpoint for specular microscopy was the mean percent loss of endothelial cell density

at 12 months postop; in other words, the average of the individual percent loss. The statistical analysis called for in the protocol was to demonstrate that for the population, the mean percent loss in ECD was no greater than 17 percent.

Why was the figure of 17 percent chosen by the sponsor? In the IDE stage, the sponsor did a review of the literature. In published studies they found that a mean ECD loss of 10 to 17 percent within 1 year postop was observed for large incision surgeries. The FDA agreed that the 17 percent was a reasonable target for the protocol.

The surgery-related decline at 12 months postop was 25 percent for the all IMT-implanted cohort; thus, they failed to reject the no hypothesis. Now the protocol didn't really call for looking at these different subgroups, but the decline at 12 months for the sub-cohorts was 24 percent for the guttata free large ACD sub-cohort and 19 percent for sub-cohort A.

The distribution of ECDs changed in three ways from preop to postop. First, there was a lowering of the mean ECD. Second, there was a skewing of the distribution toward lower values, and third, there was a large increase in variance.

The second row of this table shows the mean ECDs over time for the all implanted cohort. You can see that the means dropped rapidly in the early postop stage of the study, 22 percent at 6 months, and then continued to drop at a much lower rate over time. Each figure in the bottom row represents the percent change in the mean from the prior 6 month visit. However, the mean for each time point represents a slightly different subset of eyes that were available. Note that the 60-month figure in this table represents data from only 17 eyes.

Understanding this slide is one of the keys to understanding some of the safety issues related to ECD changes. In this figure, you can see the significant drop in the mean early in the study, but you also see the large postop increase in the spread of the data. I wish I had a pointer here, but you can see that there's a lot of eyes down toward the bottom there after surgery. What this figure doesn't show is that the preop distribution had a fairly normal shape, while the postop distribution was skewed toward lower values.

We do have a figure in our executive summary showing the skewing of the distribution? So you can look that up later at your leisure.

Because of the skewing toward lower values and the increased variance, it is important not to look only at the mean changes. If the sample had suffered a mean 25 percent ECD drop, without the increase in the spread and the skewing of the distribution, there would have been significantly fewer eyes at low ECD levels.

A significant number of eyes had very low postop cell counts. The bottom row of this table shows the number of percent of eyes at each visit that had ECDs less than 1,000. At 12 months postop, 11 percent of the eyes seen at that visit were below 1,000. There were significant changes in counts from visit to visit partly because of the low precision in the ECD measurement in this population.

This figure on the left shows how for some implanted eyes the ECD measurements bounced around considerably from visit to visit. The cause of poor reproducibility is uncertain, but we believe that it may be related to poor patient fixation during specular microscopy in patients with macular problems.

This bouncing around of the data from visit to visit made analysis of the data somewhat problematic, and we took several different approaches

to looking at the data.

We're now going to move on and discuss the chronic ECD loss. The sponsor used a statistical regression model to characterize certain aspects of the ECD loss. The question arises why use a statistical model at all? A statistical model smoothes out bumps in the ECD data. We've seen graphs of the ECD data over time that kind goes up and down a little bit. It reduces the problem of having different subsets of patients available at different visits, and it permits the simplest estimation of a constant chronic loss rate using all of the data rather than just a subset.

In some of the analyses that have been presented earlier, the loss between two time points was presented. Because many eyes were unavailable for later time points, these types of analyses use a restricted sample of the study eyes that were available at both time points.

There are advantages to modeling, but keep in mind that modeling only estimates an average rate of decline and is based upon certain artificial mathematical assumptions.

A biexponential model was introduced by the sponsor subsequent to the 2006 Panel meeting. This

type of model had been used in previously published articles in the literature. It does not require establishing a breakpoint between the time of surgical loss and the time of chronic loss. My colleague, Dr. Huang, will discuss some of the technical details of this model later.

The sponsor used the biexponential model to estimate the chronic rate of loss. Here you can see for the all implanted group, the chronic rate was 4.8 percent per year. The upper confidence limit on that was 6.2 percent. This 4.8 percent chronic loss is in contrast to the 3 percent chronic rate cited in one of the earlier presentations. The 3 percent is based upon a paired analysis of approximately 85 eyes at two different time points.

For the restricted sub-cohorts, the rates were 3.8 percent for the guttata-free large ACD sub-cohort and 3.4 percent for sub-cohort A.

The sponsor has proposed a contraindication for preop ECDs below minimum baseline values for each age and gender group. This grid of minimum values for each group assumes the need for an end-of-life ECD of 750 cells per square millimeter. The grid was developed by back-calculating the minimum baseline values using the upper 90 percent confidence limit on

the chronic rate of loss. This was estimated from the biexponential model. It assumes an average life span stratified by gender.

For the grid proposed by the sponsor, they used the results from the biexponential modeling of the guttata-free large ACD sub-cohort. They applied the model to the data available through 48 months postop. This sub-cohort had 112 to 95 available eyes in the initial 24-month phase of the study and a maximum of 50 available eyes with ECD data at any visit in the post-24-month phase of the study. The mean ECD at 12 months was estimated by using the model. The estimate of the ECD at this time point was 1954 cells per square millimeter. The lower 90 percent confidence limit on this mean was calculated and used to represent the loss at one year. This yielded a 24.6 percent one year loss from baseline. The chronic loss from the biexponential model was 3.8 percent per year. The upper 90 percent confidence limit on this rate of loss was 5.5 percent per year. This number was used to estimate the losses for each year after the first.

This figure helps clarify how the minimum baseline ECD was determined. It shows an example for the group of 65 to 69-year-old males. This group had

an average life span of 16.6 years. So the sponsor started with the assumption that at 17 years after surgery, the eye needed an ECD of at least 750. Then for the year prior to that, a loss of 5.5 percent was assumed and the number of 794 was calculated.

This type of calculation assuming 5.5 percent drop was repeated for each year until the first year postop. For the first year, a drop of 24.6 percent was assumed and the baseline ECD of 2460 was calculated.

The FDA requested calculation of an alternative grid based upon biexponential modeling of baseline to 48-month data for the all IMT-implanted cohort. This unselected group contained 206 eyes at baseline, had 171 eyes available at 24 months, and had a maximum of 101 ECD measurements at any visit between 30 and 48 months. Calculations for this grid were done in a manner similar to those for the previously discussed version of the grid.

In this case, a 26.3 percent first year loss was assumed and an annual chronic ECD loss of 6.2 percent was used. The 6.2 percent represents the upper 90 percent confidence limit on the estimate of 4.8 percent per year.

Here we present the two grids that have

been constructed for possible contraindication, laying out minimum preop ECDs. The first proposed by the sponsor is based upon the guttata-free large ACD sub-cohort. The second is based upon the all IMT-implanted cohort.

The two are virtually the same for patients greater than or equal to 75 years of age. It is in the lower age groups that there are significant differences. For example, for 65-year-old males, the sponsor proposed grid requires a minimum ECD of 2460 while the alternative grid requires a minimum of 2834 cells per square millimeter. Differences are even higher for females.

The Panel will be asked to provide the recommendations concerning the appropriate structure of the grid. In particular, they should discuss whether an end-of-life ECD of 750 cells per square millimeter should be regarded as sufficient to prevent corneal decompensation. In discussing the appropriate structure of the grid, the Panel should consider the following relevant facts. IMT patients will not routinely require another intraocular surgery. IMT removal, if needed, may cause significant surgical trauma and the grid is based upon estimates of average rates of cell loss.

There's poor predictability of postop ECD from baseline measurements for individual eyes. This last point is illustrated in the following slide.

In this graph, the X axis is the preop ECD measurement, and the Y axis is the 24-month ECD. All 171 eyes with ECD measurements at both of these time points have been placed in a scatterplot. As you can see, there's a large dispersion of the data about the regression line, implying that postop ECD is pretty unpredictable from the preop ECD. The regression R squared is 0.18. The point of this is that even eyes -- let me see if I can point here. Even eyes that start the study with high cell counts, there can be a significant chance of ending up with quite low ECDs two years later.

The sponsor's constructed two grids for determination of minimum preoperative ECD for various age and gender groups. Both grids are based upon calculations assuming an end-of-life ECD of 750 cells per square millimeter.

Our questions are as follows: Is the assumption of an end-of-life ECD of 750 cells per square millimeter acceptable? If not, what do you believe is appropriate?

One of the grids is based on the ECD

changes in a sub-cohort of 112 eyes, guttata-free eyes, with an 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. Which grid do you recommend for labeling contraindications for the currently proposed patient population? Please discuss your reasons for choosing one or the other.

There are two measures of regularity in endothelial size or shape that can be assessed from specular microscopy images. Coefficient of variation is a measure of irregularity in cell area. Increases, which are generally considered undesirable, indicate greater irregularity. The percent hexagonality is a measure of regularity of cell shape. Decreases, which are undesirable, indicate greater irregularity.

It is sometimes said that reduction in percent hexagonality and increase in coefficient of variation imply continuing rapid cell loss and that return to normal levels may reflect increasing stability of the endothelial layer.

The 2006 Panel and subsequently FDA requested morphometric analysis of the available specular microscopy data. There was no morphometric

data presented at that Panel meeting. This was requested in order to aid in assessing whether the endothelial cell layer had stabilized.

This table shows the mean coefficient of variation over time for a consistent cohort of IMT-implanted eyes. It is apparent that there were only small changes in the mean values. The sponsor has stated their belief that a coefficient of variation greater than 45 indicates a stressed endothelium. You can see that there were few eyes that were stressed according to this criterion.

This is a similar table showing the percent hexagonality over time. Again, there were only small changes in mean values with a minor dip at three months which subsequently reversed and later approached baseline levels. Sponsor has stated their belief that a percent hexagonality less than 45 implies a stressed endothelium. You can see that there were relatively few eyes that were stressed according to this criterion.

In interpretation of the relatively positive morphometric analyses, the following should be considered. No morphometric data are available for the corneal periphery as specular microscopy was only done centrally. Therefore, it is unknown

whether the CV and percent hexagonality were normal or abnormal in the periphery. Mean ECDs continued to drop significantly after 24 months postoperatively. For example, ECDs dropped an average of 6 percent in 86 IMT eyes with visits available at 24 and 48 months. Several new incidents of corneal edema continued to occur well after the initial surgery, and CV and percent hexagonality seem to show little predictive value in this patient population. This is discussed further in the next slide.

On this graph, the X axis is the percent hexagonality at 24 months, and the Y axis is the ECD percent change from 24 to 48 months. All IMT-implanted eyes with data from both visits are shown in this scatterplot. If the percent hexagonality at 24 months were indicative of endothelial stability, you might expect eyes with lower percent hexagonality would tend to have more negative percent change in ECD over the next 2 years. However, there's no indication of such a pattern here. Changes in ECD between 24 and 48 months in this patient population appear to be unrelated to the measured percent hexagonality at 24 months.

This graph is similar to the previous one except that the X axis is CV at 24 months. This

graph shows the percent change in ECD from 24 to 48 months as a function of the CV at 24 months. If the CV at 24 months were indicative of endothelial stability, you might expect that eyes with higher CV would tend to have more negative percent change in the ECD over the next two years. There's a slight tendency toward this relationship shown in the graph, but it seems to be largely driven by a couple of eyes with very low CV. All in all, the changes in ECD between 24 and 48 months in this patient population appear to be largely unrelated to the measured CV at 24 months.

We're now going to go on to discuss the risk of corneal edema. Corneal edema at greater than 3 months postop was observed in 13 eyes in the study. One of these cases was in a non-implanted eye. The remaining 12 cases were in IMT-implanted eyes. Ten of these twelve were observed at 24 months or later.

In 3 of the 12 cases, in IMT-implanted eyes, the edema was reported to have resolved. In two of these three eyes, the etiology was believed by the medical monitor to be inflammatory or partly inflammatory in nature. In one case, subject 012-212, the edema was reported as resolved after duration of 196 days. However, the central corneal

thickness remains significantly increased from baseline at the last available visit. Two of these three eyes that are reported as resolved had ECDs of less than 1,000 at some point in the study.

There were 9 IMT-implanted eyes with unresolved corneal edema at the last available visit. There were six cases reported by the sponsor as decompensations. Four of these had transplants and two did not. The latter two subjects died within one year after the decompensations. Two of the transplant cases also had explantations of the IMT. There were three additional cases reported as having unresolved corneal edema. All of these were associated with low ECDs.

Here we show the number and percentage of eyes that had unresolved corneal edema at the last available observation. Note that the last available observation may be different for each eye, potentially somewhere between 9 months and 60 months. For the all IMT-implanted, there were 9 cases of unresolved edema which represents 4.4 percent of the 206 implanted eyes. This number does not count subject 012-212 reported with resolution of edema but continuing increased central corneal thickness.

The upper confidence limit on the

percentage is 8.1 percent. The upper confidence limit can be thought of as a measure of the level of assurance that the study data has provided for this aspect of safety.

The next two rows show the results for the two sub-cohorts we have described. The 112 guttata-free large ACD sub-cohort had 2 cases of unresolved edema representing 1.8 percent. If you assume that the entire study had been only these 112 eyes, then the upper confidence limit on the percentage would be 6.3 percent. Sub-cohort A also had 2 cases of unresolved edema representing 6.1 percent of this risk-reduced sub-cohort. The upper confidence limit on this percentage is 20.2 percent.

This slide shows the times that edema was observed for all eyes with unresolved edema in the all IMT-implanted cohort. This chart includes case 012-212 whose edema was reported as resolved but whose central corneal thickness remains increased. The X axis shows time postop, and the Y axis is simply the subject number. Each horizontal bar shows the time span for which edema was reported for that subject. So basically these bars were created by taking the time that edema was first reported for that subject, and then end of the bar is the last

available time for that subject.

We can see that there were a few cases with edema occurring relatively early in the study but quite a few in which the edema came significantly after the immediate postop months. One eye had an edema of first observed at 54 months postop. Note that in the initial IMT-002 phase of the study, there were more total eyes available for observation than in the LTM phase of the study.

We're now going to move on to talk about the eyes in the study that had low ECDs at their last available observation. These last available observations varied in time, in postop time, from eye to eye with the potential to vary from 3 months to 60 months. This table is similar to the previously shown table on corneal edema, but here we're looking at the number of eyes with last visit ECD less than 750 cells per square millimeter.

For the all IMT-implanted cohort, there were 19 eyes with final ECD less than 750. One of these eyes had ECD less than 750 only after IMT explantation. These 19 eyes represent 9.2 percent of the 206 implanted eyes. The upper confidence limit was 14 percent.

For the guttata-free large ACD sub-cohort,

there were 7 eyes with final ECD less than 750. These were 6.3 percent of the 112 eyes in the sub-cohort. The upper confidence limit was 12.5 percent.

For sub-cohort A, there were 2 eyes with final ECD less than 750. This represents 6.1 percent of the sub-cohort. The upper confidence limit was 20.2 percent. We note that fellow eyes of the all IMT-implanted had 2 cases of final ECD less than 750. However, this comparison has to be interpreted with caution because fellow eyes had no exclusion based upon low preop ECD. In fact, one of the fellow eyes had baseline ECD less than 750.

This table is just like the prior slide except that it shows the number of eyes with last visit ECD less than 1,000. For the all IMT-implanted cohort, there were 31 eyes with final ECD less than 1,000. These 31 eyes represent 15 percent of the 206 implanted eyes. The upper confidence limit is 20.7 percent.

For the guttata-free large ACD sub-cohort, there were 11 eyes with final ECD less than 1,000. These were 9.8 percent of the 112 eyes in the sub-cohort. The upper confidence limit is 16.9. For the sub-cohort A, there were 2 eyes with final ECD less than 1,000. This represents 6.1 percent of the sub-

cohort, and the upper confidence limit on that is 20.2 percent.

Fellow eyes of the all IMT-implanted had 5 cases of final ECD less than 1,000. Again, several of these fellow eyes had baseline preop ECDs of less than 1200.

This slide provides some idea when the ECDs declined to low levels. For the 18 eyes with final ECD less than 750 cells per square millimeter, this graph shows the times in the study when the counts first dropped below 750. The bar for each visit represents the number of these eyes that first drop below 750 at that visit. Note that, although the X axis shows time postop, it is not drawn to scale. The early bar is being drawn for every three-month visit while the lateral ones are drawn for every six-month visit.

This graph shows that most of these declines started relatively early in the study. There were relatively few in the LTM phase of the study, but one of these declines occurred as late as 54 months postop.

This slide clarifies the relationship -- I know this looks ridiculously impossible, but bear with me. This slide clarifies the relationship

between the low ECD levels and some serious adverse events seen in the study. This matrix shows every eye that had either a final visit ECD less than 1,000, a case of unresolved edema, or an IMT explant. There were 41 eyes in the IMT-implanted cohort that had at least one of these events. This represents approximately 20 percent of the IMT-implanted eyes.

In the top row, I've provided subject numbers from 1 to 41 for these subjects. The dot dot dot symbols in the top row there just mean and so on, because I did not have enough room to show every subject number. The second row shows the 9 IMT-implanted subjects with unresolved corneal edema. The third row shows the 12 subjects with device explants. The fourth row shows the 31 subjects with final ECD less than 1,000.

So, for example, subject number 4 had final ECD less than 1,000, had unresolved edema, and had the IMT explanted.

All of the nine eyes with unresolved edema, except for one, also had low cell counts. This one eye did not have a low central count until after a secondary surgical intervention. Two of these nine eyes also had the IMT explanted.

For the other 10 explants, only 1 eye had a

final ECD less than 1,000, and in this eye, the ECD dropped low only after the IMT was explanted. These 10 eyes had explants only because of patient dissatisfaction or device failure.

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 morphometric 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: please discuss whether the ECD and morphometric data provide reasonable assurance that the long-term risk of corneal decompensation will be acceptable for the intended population. Please discuss whether the specular microscopy data provide sufficient characterization of long-term ECD trends.

Thank you for your attention. We're now going to have Dr. Huang, a statistician who worked on the project.

DR. HUANG: Good afternoon. My name is Yao Huang from the Division of Biostatistics at CDRH FDA. I am one of the statistic reviewers of this PMA.

Today I will make some comments on the PMA concerning the Implantable Miniature Telescope from a statistical perspective.

And this is the outline of my talk. First, I will present some results for the safety endpoint concerning long-term endothelial cell density loss. Second, I will give an introduction of the biexponential model that the sponsor used, and I will present some results from this model. Then I will address the caveats associated with the data extrapolation, and I will also discuss about the concerns about subgroup analyses. Then I will wrap up my talk with a brief summary.

And here, since the Panel meeting in 2006, we have revisited the primary safety endpoint since more follow-up data became available. The sponsor performed various subgroup analyses in order to identify patient subpopulation that may provide the safest long-term ECD profile.

And the primary safety endpoint is that the mean percentage ECD loss at 12 months post surgery, the non-hypothesis is that the mean percentage ECD loss at 12 months is no less than 17 percent. It is found that for all IMT-implanted eyes, the observed rate is 25.5 percent with a 95 percent confidence

interval from 22.1 percent to 28.2 percent. The non-hypothesis cannot be rejected.

By conducting various post hoc subgroup analyses, the sponsor proposed one subpopulation for device indication that requires the patients are at least 65 years of age with ACD no less than 3.0 millimeters and guttata-free. And the sponsor intends to use this subgroup as the basis for the proposed ECD grid for implantation eligibility.

Among the 206 IMT-implanted eyes, 99 eyes belong to this proposed subgroup, and the observed ECD percentage loss is 23 percent and its 95 percent confidence interval ranges from 19 percent to 28 percent. Again, the non-hypothesis cannot be rejected. That means the safety endpoint is not met among the proposed post hoc subpopulation.

And here I would like to give some introduction about the biexponential model, and in order to evaluate long-term ECD loss, the sponsor proposed a biexponential model which can be described by this formula. On the left-hand side, ECD stands for the counts of endothelial cells at time t, since device implantation. On the right-hand side, the first term is used to describe the rapid rate of ECD loss associated with surgery. The second term is to

describe the slow rate of ECD loss after stabilization.

This table provides the estimated annual ECD loss based on the biexponential model that was introduced in the previous slide. The biexponential model was fitted using the 48-month ECD data, and I would like to point out that these numbers were obtained through the second term of the biexponential model, that is, the slow rate of ECD loss after stabilization.

The numbers quoted here are the sponsor's estimates, and the first row is for all IMT-implanted eyes, and the second row is for eyes from the selected sub-cohort with a large ACD and guttata-free. It is noted that 112 IMT-implanted eyes belong to this subgroup. It is noted that the cohort of all IMT-implanted eyes have larger annual ECD loss compared to the subgroup. However, the 90 percent confidence intervals have large overlap, and the estimates in annual ECD loss do not appear to differ statistically.

And this is the proposed grid of preoperative ECD required for IMT implantation based on data of the IMT-implanted eyes without guttata and large ACD. Dr. Hilmantel has introduced the

calculation of this grid. Here I want to point out that this grid is generated by extrapolating the biexponential model, and we can see that some extrapolation is as far as more than 20 years.

In order to create the grid, to address the long-term ECD profile after surgery, the sponsor conducted data extrapolation based on 48-month data. That means the sponsor tried to use four years data to predict the device performance in more than 20 years. However, data extrapolation beyond the range of the current dataset should only be done with extreme caution because of these reasons. The current model may not fit outside the range of the available dataset. Data extrapolation is very sensitive to variability of the estimates. Such sensitivities increase the further we extrapolate.

In order to understand the variability of the ECD measurement over time and within patients, let's take a look the raw ECD data from the clinical trial. For illustrations purpose, random samples are selected from the IMT-implanted eyes and the fellow eyes. It is also noted that there is large variation in ECD measurements from eye to eye. It is also noted that patients starting with high ECD at baseline tend to remain a relatively high ECD level

throughout the study, which shows that there is some correlation within patients over time. So the sponsor's assumption of data independence within eyes may not reflect the true ECD relationship among patients over time, and this is one limitation of the biexponential model. Therefore, the confidence bounds of the proposed ECD grid may not be very well validated.

This plot shows the actual ECD measurements of all IMT-implanted eyes through 48 months postoperatively. The black curve stands for the fitted biexponential model for IMT-implanted eyes, the red curve for the eyes of the sub-cohort with ACD no less than 3.0 millimeters and guttata-free. The horizontal axis is time in months starting from surgery and the vertical axis is the ECD counts. It is noted that there is huge variation in ECD measurement, and despite that, the red curve shows relatively better ECD profile. The difference between the two curves is actually very little.

So the major statistical concerns for this PMA are unplanned subgroup analyses should always be interpreted with caution. Repeatability is of serious concern for the proposed sub-cohort. Therefore, we want to ask, are these differences

between different patient cohorts clinically meaningful? And, if so, are the differences repeatable?

In summary, the study did not meet the safety endpoint of ECD loss at 12 months postoperatively, nor did the selected sub-cohort. Grave caution is needed when conducting data extrapolation. The sponsor's assumption of data independence in ECD measurements over time and across patients may not reflect the true trend of ECD loss over time. The results from the sub-cohort analysis may not be repeatable.

Therefore, our question for the Panel 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, do the data constitute valid scientific evidence for evaluation of safety of this device?

Thank you very much.

DR. HILMANTEL: We're now going to have Dr. Michele Bonhomme, our epidemiologist from the Office of Surveillance and Biometrics.

DR. BONHOMME: Good morning, Dr. Weiss, distinguished Panel members and guests.

My name is Michele Bonhomme, and I'm a team leader in the Division of Epidemiology in the Office of Surveillance and Biometrics. The sponsor has discussed their postapproval plans with FDA, and I will be presenting an assessment of those plans.

First I will discuss the postmarket concerns about the IMT. Next, I will give an overview of the sponsor's postapproval study proposal. I will then discuss FDA's assessment of that proposal and will conclude with a summary of the issues that we would like the Panel to discuss.

There are a few points we would like you to keep in mind as you consider the postapproval plans for the IMT. First, please be reminded that the discussion of the postapproval study prior to the formal recommendation on the approvability of this PMA shouldn't be interpreted to mean that FDA is suggesting that the Panel find the device approvable. Second, the plan to conduct a postapproval study does not decrease the threshold of evidence required to find the device approvable. And third, the premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

There are two general principles for postapproval studies. The primary purpose of conducting postapproval studies is to evaluate the device performance and potential device-related problems in a broader population over an extended period of time after the premarket establishment of reasonable device safety and effectiveness.

Postapproval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

And you heard earlier from Dr. Marinac-Dabic a description of the needs for the postapproval study, and I would just like to recap those for you. Generally, the reasons for conducting postapproval studies are to gather postmarket information including the long-term performance of the device, to gather information on the real world experience when a broader patient population is treated by average physicians, and this is in contrast to the highly selected patients that are treated by leading physicians in the clinical trials. And in considering the real world experience with the device, it's also important to monitor device-associated adverse events, especially rare events

that were not observed in the clinical trial.

Postapproval studies can also be used to evaluate the effectiveness of device utilization training programs and to evaluate the device performance in subgroups of patients since clinical trials tend to have limited numbers of patients and may not include all the subgroups in the general patient population.

The FDA review team identified four postmarket concerns about the IMT. These concerns relate to the knowledge that we currently lack about what the real world experience is with the IMT and what its longer-term safety and effectiveness would be if the device were approved.

First, we don't know what the longer-term risk of ECD loss is that fall below the threshold where corneal function in IMT-implanted eyes is irreversibly compromised. Second, the risk of failed implantations is unknown. Third, we need to know the risk of removals, replacements, repositionings, and device failures. And finally, the risk that the improvements in visual acuity achieved with IMT implantation is not sustained.

Having reviewed the postmarket concerns, I would now like to describe the sponsor's postapproval

plans. At the time of the July 2006 Panel meeting, the sponsor had submitted protocols for two postapproval studies. The first was the long-term monitoring study to follow subjects in the all IMT-implanted eyes cohort through their fifth year post implant. The second protocol was for a study design to follow for five years after implant, a newly enrolled cohort of IMT patients who received the device in the postmarket environment.

On February 6th of this year, the sponsor indicated that it believes that a postapproval study is not necessary because most of the subjects in the long-term monitoring study have completed their 48 month exam. We will ask the Panel to comment on the need for a postapproval study. To address the possibility that a postapproval study may be recommended, however, the sponsor submitted the IMT-002-LTME protocol for consideration. Under that protocol, the subjects in the all IMT-implanted eyes cohort would be followed for two additional years for a total of seven years.

Let's look at the main features of the proposed study. The objective would be to monitor the long-term safety of the IMT in the all IMT-implanted eyes. The study design is described as a

prospective study and as a non-comparative descriptive study. The population consists of subjects in the all IMT eyes cohort including, but not limited to, the subjects who participated in the long-term monitoring study. The draft protocol doesn't specify a study size. As I mentioned earlier, the duration of follow-up would be two years. The subjects would be evaluated at 72 and 84 months, and if the study entry occurs outside of the window for those two examinations, then the patients would be evaluated at study entry also.

The primary endpoint is not specified but the clinical parameters to be assessed in subjects are listed here. There's no hypothesis specified for the study, and the statistical analyses will consist of descriptive techniques using 95 percent confidence intervals, and the sponsor's rationale is that due to the study is observational and non-comparative.

Now that you've heard a brief description of the sponsor's plans, I'd like to present the FDA assessment of the proposed plans. The protocol describes the study as a prospective study, and in the statistical analysis section, as a non-comparative, descriptive study. The protocol also states that ECD and best-corrected distance visual

acuity will be assessed in fellow eyes, and the percent change in ECD is one of the clinical parameters. So we would consider the study to be comparative since fellow eyes will be used as controls for the IMT eyes.

As I mentioned before, the population is the all IMT eyes cohort. The potential bias in the study results and the adequacy of the study size are a concern. The study size will depend on the number of subjects in the all IMT eyes cohort who are recontacted and reconsented.

One concern is that losses to follow-up to date and the willingness of subjects to participate will impact enrollment rates. Study results may be biased if participation is related to outcomes at the time of recruitment. For example, subjects who are dissatisfied with the device may be more likely to refuse, and the clinical sites' recruitment efforts may also vary by patient status and IMT outcome. A second concern is that losses to follow-up during the two additional years of follow-up may also introduce bias if losses are influenced by the IMT outcome. Third, the absence of 36 and 48 month data from members of the all IMT eyes cohort, who did not participate in the long-term monitoring study, is

also a concern. In summary, the use of the all IMT eyes cohort in the proposed postapproval study may lead to biased results that may not be generalizable to the eligible patient population.

I'd like to elaborate on the point of generalizability of the results for the proposed study. As the statistician noted, close to half of the 206 IMT-implanted eyes had at least one of the contraindications specified in the currently proposed indication. So there's a concern that the results for the all IMT eyes cohort cannot be generalized to the eligible population based on the proposed indication.

The number of subjects available for analysis at seven years should be large enough to detect small but clinically significant ECD changes. The primary safety endpoint should drive the study size and the power calculations.

The proposed ECD endpoints are listed here. We would recommend at least three other endpoints, the relative risk of any corneal edema, of late corneal edema, and decompensation. The relative risk would be based on a comparison of IMT and fellow eyes or perhaps another appropriate control group. This might address Dr. Ferris' comment this morning about

being able to tell a patient what the excess risk of corneal edema and corneal transplants might be.

There's a 12-month interval between the 72 and 84-month visit. The interval between examinations in the long-term monitoring study was 6 months. So we will need to consider whether there are any adverse clinical consequences of not detecting clinically significant ECD changes in that interval.

The current draft of the proposed protocol does not specify a hypothesis. However, the study design allows for comparison of ECD changes over time in the same eye and differences between IMT and fellow eyes. A statistical hypothesis increases the scientific rigor and public health utility of postapproval studies. So if the device is approved and a postapproval study is recommended, we will work with the sponsor to define the hypotheses.

The current protocol only states that statistical analyses will consist of descriptive techniques using 95 percent confidence intervals. If the PMA is approved, and a postapproval study is recommended, we will encourage the sponsor to provide a more detailed analytic plan. The detailed plan might include the calculation of relative risks for

certain parameters such as ECD below a certain threshold level, device survival analyses, and plans for evaluating and handling missing values. A sensitivity analysis could also be performed to evaluate the impact of missing values on the study results.

Now I will present the questions that FDA would like the Panel to consider during its afternoon deliberations.

Before presenting the specific questions which are labeled a through d, I would like to read an introductory statement that describes again the sponsor's postapproval plans in 2006 and those presented this year.

A five-year postapproval study following up the IMT-002 patients was proposed in the IMT-002 patients. The second study would be a follow-up study of newly enrolled patients who received the device after approval, and they would be followed out to five years.

As I mentioned before, on February 6th, the sponsored indicated that they did not believe a postapproval study is warranted at this point because most subjects in the IMT-002 long-term monitoring study have reached their four-year follow-up

examination. However, to address the possibility that a postapproval study might be recommended, the sponsor did submit a protocol for our consideration.

Given the currently available safety and effectiveness data, and if this device is approved, is a postapproval study recommended?

If a postapproval study is recommended, does the Panel agree with the sponsor's proposal to follow the currently implanted patients out to seven years? If not, what do you recommend?

And, c, is a postapproval study of newly enrolled patients needed to evaluate the performance of the device when used in the postmarket environment?

And finally, d, if a postapproval study is recommended, what do you recommend for the following postapproval study elements? These include the objectives, the clinical endpoints, the clinically tolerable rates of severe events such as corneal decompensation-induced device extractions and corneal transplants, the duration of follow-up for the study subjects and I would also add the choice of a control group, and any other specific issues that you would like the postapproval study to address.

This concludes my presentation and the

FDA's morning presentations. We welcome your questions.

DR. WEISS: I'd like to thank the FDA speakers for their very excellent and clear presentations. We're going to have 15 to 20 minutes of questions from the Panel to the speakers.

Dr. Matoba.

DR. MATOBA: I'd like to ask Dr. Lepri a question, and it's about -- it's the one on the side effectiveness degree of visual improvement at 12 months compared to baseline, that slide.

DR. LEPRI: Yes.

DR. MATOBA: Okay. I guess I don't understand it, but for that first group, the 20/80 to 20/160, when it says 3.6 percent improved -- well, I mean how many people are really in that group and how many people actually improved? And it seems to indicate that you have like a 50 percent chance of being worse I mean compared to being better.

DR. LEPRI: In the moderate impairment group at baseline where 20/80 to 20/160.

DR. MATOBA: Yeah.

DR. LEPRI: That's the group you're referring to. It only showed that 3.6 percent of them improved.

DR. MATOBA: Of them.

DR. LEPRI: Of them.

DR. WEISS: Would it be helpful for you to have the slide or would it be easy to get the slide up there?

DR. LEPRI: I have the slide right here. I was just --

DR. MATOBA: So you had some 30 -- how many people were in the group?

DR. LEPRI: That we can look up, but I don't know.

DR. MATOBA: Okay. And then 2.1 percent got -- had worse vision?

DR. LEPRI: Yes.

DR. EDRINGTON: That doesn't add up to 100 percent.

DR. MATOBA: Pardon me.

DR. EDRINGTON: It doesn't add up to 100 percent.

DR. LEPRI: There's a mistake. This was in the degree of visual impairment.

DR. MATOBA: Right, right. Okay.

DR. LEPRI: Yeah.

DR. MATOBA: So was there not previous discussion about how this group might have the most

to gain but actually you're seeing --

DR. WEISS: I see the sponsor wants to make a comment --

DR. MATOBA: Yeah.

DR. WEISS: -- but typically this would be -- I'm going to defer -- this is typically for questions to FDA. So we're going to -- you can hold your comment. We can get back to it.

DR. MATOBA: It might be helpful though to --

DR. WEISS: It's not the time.

DR. MUSCH: We were privy to information earlier today that showed 20 percent of this group had a three line or better improvement and 86 percent of this group had a two line or better improvement. So this is a whole different criterion I think you're using for improvement.

DR. LEPRI: Well, this was in the sponsor's -- not this table. We took this from there, and the point of the entire table was to show that 75 percent of them improved, 21 percent remained unchanged, and 2.6 percent in degree of vision impairment were slightly worse. The degree of vision impairment, of course, is going to be relative to any changes in the degree of macular degeneration. It

was not caused by the IMT.

DR. WEISS: Dr. Eydelman.

DR. EYDELMAN: Perhaps after the break, the sponsor can comment as well on this point. I understand this time is restricted specifically to FDA. However, we welcome sponsor's comment after the break.

DR. WEISS: And then also what I would caution the Panel, and I think we all understand this at this point, there are many different denominators we're dealing with here and a tremendous number of different groups. So maybe each time we can talk about what the denominator is and what the group is because that is a part where it is easy to get a bit lost. Yes.

DR. SUNNESS: Janet Sunness. I think that's an issue and this thing is -- I looked at it. I think it's more like an end rather than a percentage. I think the sum of the whole chart is 100 percent.

DR. LEPRI: You're right. The sum of the whole chart is 100 percent, and the chart that the sponsor presented was very large and complicated, and we tried to boil it down as much as possible to be able to fit it on a slide. But it's the entire chart

that adds up to 100 percent, not each individual line across.

DR. MATOBA: Right. So I'm not so much concerned about what criteria we're calling improved or not improved, but I took one percent were worse. So -- whereas that's not true for the other subsets. So I guess in talking to patients in that category, how you presented the potential benefits, you know, or risk of having -- but I think we just need more comments from the sponsor later, I think.

DR. LEPRI: Yes.

DR. WEISS: I had a question about one of the -- the grid comparison in terms of the minimal endothelial cell count proposed by the sponsor and the requested alternative. I just wanted to confirm that the, A, the one proposed by the sponsor is the one which is no guttata and ACD greater than 3 millimeters as opposed to the one which is just having higher endothelial cell counts but taking all possibilities.

DR. LEPRI: Yes.

DR. WEISS: Now the other thing that I found interesting is the requested alternative, which the FDA alternative has the same -- does that -- that does not include -- does that include patients with

no guttata and ACD greater than 3, or it's all comers?

DR. HILMANTEL: I'm Gene Hilmantel. A is just the guttata-free large ACD sub-cohort, and B is the all implanted, all the implanted eyes; the data was calculated from all implanted eyes.

DR. WEISS: So what I find interesting is the age 65 to 69 is the same proposed endothelial cell count that the sponsor has for all comers. But the rest of the chart is a little different.

DR. EYDELMAN: Perhaps you can --

DR. HILMANTEL: No.

DR. EYDELMAN: -- point. The slide is up.

DR. WEISS: What I'm looking at is, A, proposed by the sponsor, the deeper end -- we can go back to -- yeah. The ones proposed by the sponsor is the minimal ECD in the patients with no guttata and ACD greater than 3 millimeters. The requested alternative is the one proposed by the FDA, correct? The minimal ECD decision grid from the sponsor which was their other more conservative alternative had the same cell count for the 65 to 69 group as the FDA chart but it actually -- it's virtually identical except for 75 and above, it's a little -- you require a little bit less endothelial cells than the sponsor

did.

DR. HILMANTEL: I think the sponsor will have to clarify what --

DR. WEISS: It's quite similar.

DR. HILMANTEL: Well, A is --

DR. WEISS: Is theirs.

DR. HILMANTEL: -- proposed for the labeling by the sponsor. B is what FDA has requested as an alternative possible grid for the labeling.

DR. EYDELMAN: However, I just wanted to bring a point that both grids were calculated by the sponsor.

DR. WEISS: And B is what I see here in the sponsor's proposal of a higher endothelial cell count if you didn't take out the ACD and guttata requirements. And that would make sense if they proposed. So the FDA is recommending that one be used --

DR. EYDELMAN: We're not recommending anything. What we're doing is we're bringing both to your attention and asking your recommendation.

DR. WEISS: Got it. Yes.

DR. SUNNESS: I had a couple of questions. First of all, I was wondering if during the lunch break, I would love to look at some of the fundus

images and OCTs and so forth, if they can be provided for us.

DR. WEISS: Yeah, we can't do that during the lunch break, but you can do that after 5:00 p.m. perhaps if we end by then.

DR. SUNNESS: I wanted to ask you a couple of things, and in your biexponential model, so it seems to me that P and Q should theoretically be the same number because you're taking those that are sort of baseline and going down and adjusting P and Q obviously is going to significantly modify the rates that you compute, and I was just wondering what the justification for that is.

And then the other thing is the skewing of the endothelial cell loss? How is that taken into account in everything?

DR. HILMANTEL: Well, the P and Q are not the same thing. I mean they sum up -- in the model, the two terms sum up to the predicted ECD amount. So it's a summation of the two. Let me pull up the slide.

DR. WEISS: And while you're pulling that up, Dr. Bandeen-Roche had a question that was very similar to Dr. Sunness'. So perhaps she could ask her question.

DR. BANDEEN-ROCHE: Yeah, I don't know if Dr. Huang might also be available to respond, and so, you know, as I look at the biexponential model, I'm pretty concerned about the interpretation of the long-term rate. So both components include a time term that continues on, you know, and so really the long-term rate remains a sum of both terms at any time, and I can certainly see that, you know, the one term would drop off to a lone number quite quickly, but I'm concerned as to whether, you know, using the model's characterization of the long-term rate parameter B adequately characterizes the actual rate that we see, say between the 24 and 48-month period, and so can you comment as to whether it does, whether this was compared with a simpler model like a spline model where we could unequivocally estimate that rate?

DR. HUANG: Yes. We did run a mixed effects model using a linear, a piecewise linear model. So the estimates of the ECD loss was very similar to the sponsor's estimates, I mean numerical rate.

DR. BANDEEN-ROCHE: Including the long-term rate particularly. So, in other words, parameter B or whatever, you know --

DR. HUANG: Right. Yes, yes, yes. Yeah.

DR. BANDEEN-ROCHE: Okay.

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

DR. HILMANTEL: Let me just -- this is Gene Hilmantel. Let me quickly answer the other question about the skewing of the data. That was not taken at all into account in the modeling.

DR. FERRIS: That was actually -- my comment is, with all due respect to the model and the mean, who cares? The issue is that tail and how big it is and how fast it's growing, and I don't think the model helps us much with that.

DR. MUSCH: Dave Musch. I'm going to refrain from any comments about the postapproval study, other than saying to corneal specialists, you shouldn't abbreviate it PAS because that's not something they like to see happen. We'll keep it to that.

But I do have some comments to Dr. Hilmantel, and they really echo Dr. Bandeen-Roche's request to do some basic time to event analyses when you have a discrete event, and you do have that with corneal edema. However, given the imprecision of the specular microscopy information, I'm not sure we can really rely much on that as an

approach, even though you talk about reaching a final event of whether it's 1,000 or 750 cells. It's quite evident that the next visit that subject might come with 1,250 and everybody thinks they're fine. So maybe we're looking at a measurement that we shouldn't hang our hats on as being something so definitive that it is a measure, you know, a wonderful measure of safety.

DR. HILMANTEL: Well, you're absolutely correct. For many of the patients, the measurement was very noisy. Early on we considered a survival analysis type of look at dropping below a certain level but, you know, some patients would drop below 1,000 or whatever number you would pick, and then they would bounce back up above 1,000. So we rejected that approach. For the patients that ended up below 750, I visually inspected the data, and virtually all of them had fairly consistent, over several visits, measurements below 750 or in that neighborhood, and -- I'm sorry. You had another part of your question. I don't remember what it was.

DR. MUSCH: Well, we can comment about --

DR. HILMANTEL: Looking at the proportion below a certain number.

DR. MUSCH: Yes.