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1 [Laughter]

2 DR. BULLIMORE: Based on what I have heard thus  
3 far, I am coming to the conclusion that the device is safe  
4 and it is effective. The issue of whether it is any better  
5 or whether the efficacy has been demonstrated over and above  
6 a straight deep sclerectomy -- is that the right term?

7 DR. HIGGINBOTHAM: Or trabeculectomy.

8 DR. BULLIMORE: I think that is something we  
9 should address in the labeling, and I would be willing to  
10 follow the lead of our very distinguished primary reviewers.

11 DR. SUGAR: Thank you for being brief. So, you  
12 are suggesting that we add to the labeling that -- if we  
13 approve this as a safe and effective device, we have the  
14 proviso in the labeling that efficacy greater than deep  
15 sclerectomy alone or trabeculectomy is uncertain or unknown,  
16 or the wording yet to be devised?

17 DR. BULLIMORE: Yes, somebody using the device,  
18 they are going to say "duh" but I think it is important.  
19 But based on the outcomes of intraocular pressure and  
20 reduction in number of meds, the thing seems to clearly do  
21 what it set out to do.

22 DR. SUGAR: Dr. Bandeen-Roche?

23 DR. BANDEEN-ROCHE: I am sure you have picked this  
24 up by my line of questioning but I just wanted to state so  
25 that panel members could respond and the sponsor could

1 respond, I am very uncomfortable with the limited number of  
2 surgeons for which we have evidence in terms of this  
3 procedure. It seems to me that we have good evidence that a  
4 few very skilled surgeons can use this device safely and  
5 effectively. But, especially given the fact that there is a  
6 learning curve that has been documented, at least some  
7 evidence of decent variation among physicians in the PMA,  
8 and then a late occurrence of goniopuncture, well beyond the  
9 12-month point, that is fairly substantial -- you know, I  
10 just am having a hard time reaching the standard of safety  
11 and efficacy based on the relatively limited number of  
12 providers for which we have reviewed data.

13 DR. SUGAR: Go ahead, Arthur.

14 DR. BRADLEY: Just a clarification then, your  
15 concern is regarding the safety of the procedure in the  
16 hands of other surgeons, and the sponsor suggested that the  
17 primary surgical failure would, in fact, be the standard  
18 procedure that is now done, the trabeculectomy. Could  
19 somebody perhaps clarify that? Because if that is the case,  
20 then the concern you raised is not such a significant one, I  
21 believe, but I would need somebody to comment on that.

22 DR. BANDEEN-ROCHE: My concern is in generalizing  
23 safety and efficacy from the present study to the broad  
24 practice.

25 DR. ROSENTHAL: You are quite right, and it is

1 true of every study -- just about every study that is done  
2 in which there is a difficult surgical procedure, and it is  
3 just something we have to note about the issues of teaching  
4 the surgery, making sure that people understand what they  
5 are doing, but it is certainly applicable to a large number  
6 of devices that are studied, along with the surgical  
7 manipulation.

8 DR. SUGAR: Could we not require instructional --  
9 does the agency require instructional programs for the  
10 device? Certainly with the lasers there are requirements;  
11 with keratomes there are requirements. Could we require  
12 that the sponsor either provide or mandate -- I am not  
13 saying necessarily that this is what we should conclude or  
14 not, but that is an option for purchases of the device by  
15 physicians. Ralph, I am asking you.

16 DR. ROSENTHAL: We can -- yes. I feel I answered  
17 that too briefly -- now I have lost my trend of thought --

18 DR. BANDEEN-ROCHE: In the meantime, can I just  
19 jump in?

20 DR. ROSENTHAL: I remembered it, please let me  
21 finish it because it is important. You have to put yourself  
22 in a physician's role who is out there, practicing medicine  
23 and being told that you have to blah, blah, blah. You know,  
24 it is a fine line where we interfere with things. I think  
25 with the laser we insisted that they be skilled in the use

1 of the laser -- well, number one, there was certain wording  
2 about what skills they had to have before they could use the  
3 laser. I think it was medical or surgical management of the  
4 cornea. Then, we did request that calibration issues and so  
5 forth be presented to them. As you know, there were courses  
6 mandated by the agency. I think you have to walk a fine  
7 line when you deal with the actual surgical procedure with  
8 people who are practicing ophthalmologists, and possibly  
9 should understand that this is going to be a difficult  
10 procedure and should make sure they know what they are doing  
11 before they do it.

12 DR. SUGAR: I am just trying to bring that up as  
13 an option because the procedure exists independent of the  
14 device, and the use of the device adds, I think, technically  
15 very little to the procedure. Once you have done the  
16 procedure, you sew in the device.

17 DR. BANDEEN-ROCHE: If I could just conclude by  
18 saying that my concerns are exacerbated by the lack of  
19 randomization almost at any level. A couple of the papers  
20 included randomization, not many of them did. Control  
21 procedures like blinding were not described at all. So, it  
22 is just a conglomeration.

23 DR. SUGAR: I think Jayne Weiss had a comment.

24 DR. WEISS: I was just going to reiterate what  
25 Ralph said. Ordinarily, when we are following clinical,

1 surgical innovations this is the way things are done and I  
2 think it is up to the surgeon to learn the technique, and I  
3 don't think the FDA should be mandating that, nor should the  
4 panel be making that recommendation.

5 I have another quick question though in terms of  
6 the goniopuncture. I was just trying to look up the  
7 sponsor's labeling in here, but in the U.S. study, because  
8 there was less than 12 months follow-up, which was needed to  
9 present it to FDA, there was not a high percentage of  
10 goniopuncture. But when we bring it out to five years in  
11 Switzerland, it has been reported as 50 percent of  
12 goniopuncture, should that be indicated in the labeling if  
13 this is going to be an integral part of maintaining the  
14 success of this procedure?

15 DR. SUGAR: I think that is certainly an option  
16 that we have.

17 DR. BRADLEY: Joel, I never did get an answer to  
18 my question.

19 DR. SUGAR: Remind me what your question was.

20 DR. BRADLEY: The concern was that in the hands of  
21 other surgeons this procedure might be problematic, and the  
22 sponsor made the claim that the likely surgical problem  
23 would simply be puncturing all the way through to the  
24 trabeculum meshwork, and that would effectively be the  
25 standard procedure. So, I am wondering whether the concern

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1 that was essentially a methodological concern in the design  
2 of the study is a significant one or a fairly benign one.

3 DR. SUGAR: Do you want to respond to Dr.  
4 Bradley's question?

5 DR. HIGGINBOTHAM: Yes, I have been wanting to  
6 respond for the last five minutes, Dr. Sugar.

7 DR. SUGAR: I tried to look the other way; I am  
8 sorry.

9 DR. HIGGINBOTHAM: Okay, that is all right. I  
10 still think it is a question that is worthy of discussion  
11 because a surgeon may be committed to doing the deep  
12 sclerectomy with collagen implant and not choose to use  
13 antimetabolites, such as monomycin C, which can change the  
14 ultimate outcome of the procedure. If, for instance, they  
15 did penetrate and could not use the collagen implant, then  
16 they will have to use subconjunctival injections of 5-  
17 fluorouracil. So, I think it is still a worthy issue, and  
18 it speaks to the importance and the relevance perhaps of  
19 discussing to what extent does the device add significant  
20 efficacy to the procedure. So, I just lay that at your  
21 feet, Dr. Rosenthal.

22 DR. SUGAR: Although, again, we are not  
23 necessarily discussing added efficacy; we are discussing  
24 efficacy. Dr. Newman?

25 MS. NEWMAN: I think something should be said

1 about the issue of long-term results, which I think are  
2 questionable, and then also if the device dissolves we  
3 should say something about the reuse of this, is this a one-  
4 time procedure or, if it dissolves, can

5 DR. SUGAR: Can I ask you a question? Are you  
6 talking about reuse --

7 MS. NEWMAN: Put another one in.

8 DR. SUGAR: Put another one in. Okay.

9 MS. NEWMAN: So, what this study is about is the  
10 single use of this, as far as one time done.

11 DR. SUGAR: And your point is that we don't have  
12 data available and we should make people aware of that.

13 DR. COLEMAN: One of the things that did come up,  
14 especially in Eve's review, is the issue of potential lack  
15 of efficacy in African Americans, and I do think that that  
16 should be noted in the labeling, that there has been limited  
17 experience in other races besides Caucasians.

18 DR. SUGAR: So, we are now sort of moving into  
19 package insert or labeling issues. We can continue this or  
20 we can sort of move into the questions which will then bring  
21 us back to that. Let's move into the questions. Do we need  
22 to have them projected, Dr. Lepri? While you are setting  
23 them up, we will start moving towards that. Go ahead,  
24 Arthur.

25 DR. BRADLEY: Again a general question for

1 somebody completely ignorant in this procedure. A lot of  
2 the concerns expressed this morning have been about the  
3 absence of long-term data, and for one fairly naive about  
4 these things, I wonder whether this is the standard concern  
5 we always have -- well, how do we know how it is going to  
6 perform in five or ten years because we don't have data?  
7 Or, is there something specific, is there some reason to  
8 believe that something bad could happen at two years or at  
9 three years? Do we have some mechanism, some hypothesis  
10 there, or is it just a general lack of data that we are  
11 concerned about?

12 DR. SUGAR: I think that the sponsor presented  
13 that at the end of nine months the device is no longer  
14 present and, therefore, this functions as a filtering  
15 procedure from that point on, and should be seen as that.  
16 Eve, comments?

17 DR. HIGGINBOTHAM: Dr. Bradley, I think the  
18 primary concern, at least in my opinion, is that you only  
19 have a single first time to invade the conjunctiva and that  
20 is where you have your best success for filtration surgery.  
21 So, if you choose to use a procedure that may not have the  
22 best success rate compared to others that you may have  
23 available to you, then you have actually done that patient a  
24 disservice, I think, and so I think that is why it is very  
25 important, since glaucoma is a long-term disease, a life-

1 long disease, why long-term data specifically for glaucoma  
2 as opposed to refractive surgery is so much more important.

3 DR. SUGAR: And your conclusion is, therefore --  
4 you know, continuing that argument, how do you come down,  
5 bottom line?

6 DR. HIGGINBOTHAM: I guess I would have to defer  
7 to the FDA on this, where in all of this conversation does  
8 one suggest that we get additional follow-up of the cohort  
9 so we have more long-term data to help guide clinicians.

10 DR. ROSENTHAL: The issue is you have made a  
11 cogent argument for an additional period of evaluation. It  
12 would be nice if you stated what would be considered a  
13 legitimate time that you would look at any glaucoma pressure  
14 lowering situation of surgical involvement with the device  
15 to feel comfortable, because we can't obviously go out ten  
16 years.

17 DR. HIGGINBOTHAM: I would like to also engage my  
18 co-primary reviewer in this discussion, who is an  
19 epidemiologist as well in addition to being a glaucoma  
20 specialist, but in my opinion, I would like to see at least  
21 70 percent of the cohort followed out to two years. Again,  
22 that is just a number off the top of my head, but perhaps  
23 Dr. Coleman could add a more substantive number with more  
24 solid data.

25 DR. COLEMAN: Probably not because a lot of the

1 studies that come out with drainage devices are usually one  
2 year, and those are usually the initial results people  
3 present. Then, then come back with more long-term data  
4 where you do have the success rates decreasing. By the  
5 second year a lot of times it is down -- if it was 80  
6 percent it will be down to 60 percent by the second year.  
7 So, I think two years seems to be a good follow-up time,  
8 although even at five years they are down to, like, 30 or 40  
9 percent. So, I mean it is an issue in terms of how long you  
10 are going to follow them because eventually surgery fails in  
11 glaucoma.

12 DR. ROSENTHAL: Yes, but you have to put this in  
13 perspective of what the panel's mission is, which is to  
14 determine a reasonable assurance of safety and efficacy, not  
15 necessarily to compare it with others. I mean, it is a  
16 stand-alone thing. I think from a clinician's point of view  
17 and trying to make a decision about what to subject the  
18 patient to, you are certainly quite right but I would like  
19 you to put it in perspective in terms of the mission of the  
20 panel and the mission of the FDA to deal with the problem of  
21 reasonable assurance of safety and efficacy as it stands  
22 alone in the PMA.

23 DR. SUGAR: Go ahead, Eve.

24 DR. HIGGINBOTHAM: I guess my first estimate is,  
25 in my opinion, it is a reasonable task --

1 DR. ROSENTHAL: I am sorry, I just had a brilliant  
2 suggestion given to me --

3 DR. HIGGINBOTHAM: Okay, well maybe that exceeds  
4 my brilliance --

5 DR. ROSENTHAL: No, no, I am sure it doesn't. No,  
6 nothing ever exceeds your brilliance, Dr. Higginbotham.

7 [Laughter]

8 Let me just say what was suggested because you  
9 might want to modify what you were just going to say. You  
10 can put it into a post-approval environment to ask them to  
11 look at the patients enrolled in the study for an extra  
12 year.

13 DR. HIGGINBOTHAM: And that sounds like an  
14 extremely better idea, but certainly two years with at least  
15 two-thirds of the cohort would be, I think, a reasonable  
16 thing to ask given that this is a long-term disease. I  
17 mean, ideally I would like to see ten years but I don't  
18 think that is a reasonable thing to ask.

19 DR. PULIDO: Myopia and hyperopia are long-term  
20 also, Dr. Higginbotham.

21 DR. HIGGINBOTHAM: Dr. Pulido, I am a glaucoma  
22 specialist.

23 [Laughter]

24 DR. SUGAR: I think this is degenerating so we are  
25 going to get back on track and go to question one. The

1 sponsor has proposed the following indications statement:  
2 The AquaFlow device is indicated for the reduction of  
3 intraocular pressure in patients with open-angle glaucoma  
4 uncontrolled on maximum tolerated medical therapy. Does the  
5 indication as stated adequately describe the intended action  
6 in the population for the treatment?

7 I would like to ask Dr. Coleman to address this  
8 specifically and to address a response to this.

9 DR. COLEMAN: Yes, I felt that the indication  
10 should include that it is to be used in successful non-  
11 penetrating deep sclerectomies. Even though they said that  
12 only five were not successful and had to be converted, I  
13 think it is important for clinicians to know that it does  
14 need to be successful if they want to place the collagen  
15 implant device in the procedure.

16 In addition, I felt that they should note that  
17 open-angle colleague does not include uveitic, neovascular,  
18 pseudophakic, aphakic or congenital glaucoma because these  
19 were not done in the clinical trial and had not been  
20 specifically evaluated.

21 DR. SUGAR: Could the use of the word primary  
22 open-angle glaucoma exclude those?

23 DR. COLEMAN: Yes, you could do that.

24 DR. PULIDO: It is already in the precautions  
25 though.

1 DR. COLEMAN: In the precautions?

2 DR. PULIDO: In the labeling.

3 DR. COLEMAN: Okay, but in the indication  
4 statement, is it there?

5 DR. SUGAR: No.

6 DR. COLEMAN: You could put primary; you could do  
7 that. That would emphasize it.

8 DR. HIGGINBOTHAM: I think it needs to be clearly  
9 stated that this is an adjunct to successful deep  
10 sclerectomy filtration surgery. It is an adjunctive device  
11 and by itself doesn't just lower the pressure. So, I think  
12 that clearly needs to be stated, as well as the fact that  
13 patients who were included in this study had no previous  
14 filtration surgery. So, it would have to be somewhere in  
15 the statement that patients undergoing primary filtration  
16 surgery.

17 DR. COLEMAN: Yes, I agree.

18 DR. SUGAR: So, you are saying for first surgical  
19 treatment as an adjunct in successful non-penetrating deep  
20 sclerectomies.

21 DR. COLEMAN: For primary open-angle glaucoma.

22 DR. HIGGINBOTHAM: To be more complete about this,  
23 it is no previous conjunctival surgery because none of the  
24 patients in this cohort actually had previous conjunctival  
25 invasion.

1 DR. COLEMAN: Right, because they hadn't had  
2 cataract surgery.

3 DR. PULIDO: Again, that can go into precautions.

4 DR. SUGAR: The other issue is the population for  
5 treatment. We are talking now about the types of glaucoma.  
6 The other issues is that the racial makeup of the population  
7 in the study was, you said, 78 percent Caucasian, and should  
8 there be a comment in the labeling that studies were done  
9 primarily in Caucasian populations and outcomes in large  
10 numbers of other populations are unknown?

11 DR. COLEMAN: Yes.

12 DR. ROSENTHAL: That is question three, but you  
13 don't want that in the indication statement, but you  
14 certainly want it in the labeling. Is that correct?

15 DR. COLEMAN: Yes, exactly.

16 DR. HIGGINBOTHAM: That is exactly right, Dr.  
17 Rosenthal. Thank you for that clarification.

18 DR. SUGAR: So, there is general consensus I think  
19 about the modifications of the indications and we will go  
20 back to it, or should we vote on it now? We don't have to  
21 vote on it. Sorry, I am learning.

22 DR. BANDEEN-ROCHE: Can I ask a clarifying  
23 question? We are still going to talk about other labeling  
24 indications?

25 DR. SUGAR: Yes. That is question number two. The

1 consensus is then that the indication should be -- does  
2 someone want to give more concise wording than I just gave?  
3 Jose does.

4 DR. PULIDO: I would like to give it a try. The  
5 AquaFlow device is indicated for the reduction of  
6 intraocular pressure in patients with open-angle glaucoma  
7 uncontrolled on maximum tolerated medical therapy. The  
8 success of a deep sclerectomy in the presence or absence of  
9 this device has not been clearly evaluated.

10 [Chorus of no's and laughter]

11 DR. SUGAR: I don't think there was a consensus on  
12 that.

13 DR. HIGGINBOTHAM: Dr. Sugar, is it possible that  
14 we could just defer wordsmithing to the FDA? I think this  
15 is micro-managing at this point, in all due respect.

16 DR. ROSENTHAL: We would be delighted to wordsmith  
17 it with the company.

18 DR. SUGAR: You know, no matter what we say they  
19 are going to wordsmith it anyway.

20 DR. ROSENTHAL: We know what you would like to  
21 have in the indications and we will ensure that those words  
22 are put in, except for Dr. Pulido's words.

23 [Laughter]

24 DR. SUGAR: Question number two, does the panel  
25 have any additional labeling recommendations? We have sort

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1 of accumulated a bunch of suggestions, but I would like to  
2 now try to specifically list labeling recommendations. Dr.  
3 Weiss?

4 DR. WEISS: I think there are a couple which maybe  
5 we can list under precautions, that there is no information  
6 as far as long-term follow-up of these patients, as far as  
7 the effectivity in the non-Caucasian population, as far as  
8 whether or not the procedure can be repeated successfully,  
9 in addition to Dr. Coleman's suggestions as far as  
10 stipulations, uveitic glaucoma, etc., and I don't know if we  
11 want to put in there something on the fact that  
12 goniopuncture may be necessary, or the effectivity or the  
13 necessity of goniopuncture as an adjunct -- there is no  
14 specific information on that. I would also like to add, and  
15 I think actually this may make Dr. Pulido happy --

16 DR. SUGAR: That is not necessary.

17 [Laughter]

18 DR. WEISS: -- the success of this procedure  
19 versus deep sclerectomy alone has not been compared, or  
20 there is no knowledge as to whether this has any increased  
21 efficacy over posterior sclerectomy alone.

22 DR. SUGAR: It has been compared. It has not been  
23 compared in the sponsor's presentation.

24 DR. ROSENTHAL: No, it has not been compared in  
25 the sponsor's clinical trial; it has been compared in the

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1 sponsor's presentation. They have used data from elsewhere  
2 but not as part of their clinical trial.

3 DR. PULIDO: And the data is, at best,  
4 questionable and can be interpreted either way.

5 DR. SUGAR: Consensus on Jayne's recommendations  
6 or modifications? Before we get to additional things to  
7 add, any comments on the ones that have already been stated?  
8 Arthur?

9 DR. BRADLEY: Jose's last statement, could be  
10 interpreted either way -- what did that mean?

11 DR. ROSENTHAL: One study showed it was better and  
12 the other study showed it wasn't better. I mean, you know,  
13 it is difficult to take all these things into consideration.  
14 We didn't approve the protocols for the studies. So, they  
15 have presented data but you certainly may suggest what you  
16 wish to suggest.

17 DR. HIGGINBOTHAM: I would also add that some of  
18 those patients had antimetabolites used in those other  
19 studies, just to be complete.

20 DR. SUGAR: Do you want to add anything about the  
21 issue of fornix-based flaps?

22 DR. HIGGINBOTHAM: I was waiting for your signal.

23 [Laughter]

24 Yes, under instructions for use, I think they need  
25 to specify that most of the patients had fornix-based flaps

1 as opposed to limbal-based flaps so that an interested  
2 reader could actually judge the incidence of wound leaks  
3 appropriately.

4 DR. SUGAR: Okay. Go ahead, Mike.

5 DR. GRIMMETT: I had noted five things. Some of  
6 them were mentioned in the general discussion but I want to  
7 make sure they make it into labeling. One is the steep  
8 learning curve with increased failures with early cases, as  
9 indicated on page stamped number 173 in the clinical study  
10 section.

11 Number two, the trend for decreased success in  
12 Black population, as shown on page stamped number 591,  
13 appendices section.

14 Number three, the three-fold increased success  
15 with older patients, as shown in the appendices section,  
16 page stamped 591. And, that males had a higher rate of  
17 complete success on page 592, appendices.

18 I just wanted to make a fifth comment. I don't  
19 believe that this term made it into the labeling but it is  
20 in the summary section, the term "minimally invasive" is  
21 peppered in the summary section and I object to the term.  
22 Minimally invasive implies a superiority over the standard  
23 procedure trabeculectomy, and it is possibly a way of  
24 fooling the public. Obviously, we can't control marketing  
25 issues but a minimally invasive deep sclerectomy just

1 doesn't sit well with me. I would refer those interested to  
2 an editorial, entitled, The Hamburger Institute, by George  
3 Waring, which reviews those issues. Thank you.

4 DR. SUGAR: For this subset of additions, is there  
5 a subset of conditions is there a consensus that the three  
6 issues -- you know, with Karen's review I didn't have a  
7 sense of the confidence intervals with age, race and sex.  
8 The confidence intervals were presented there and the Ns  
9 were not presented there. So, I don't know that we are in a  
10 position to assess the validity of those, or the sponsor, to  
11 specifically make those labeling issues. I am just raising  
12 that question. Mark?

13 DR. BULLIMORE: I agree with the chair on this  
14 one. I think you can't consider odds ratios in isolation;  
15 you have to consider the confidence intervals and the data  
16 there are subject to the same interpretation or  
17 misinterpretation or over-interpretation, but I think the  
18 only one that needs to be in there is the issue of we don't  
19 have enough data to make any recommendations. We don't have  
20 any data to assure that the device is as effective in  
21 minority populations, specifically non-Caucasians. I think  
22 the gender stuff and the age stuff is unclear.

23 DR. SUGAR: So, the labeling issues that we have  
24 added -- at the present, we have that there is not  
25 sufficient long-term follow-up to make recommendations

1 beyond twelve months; that the effect in non-Caucasian  
2 populations is yet unknown; that the repeatability of the  
3 procedure is as yet unknown; that data is not available for  
4 uveitic glaucoma and the other forms of congenital glaucoma,  
5 hemorrhagic glaucoma. Goniopuncture may be necessary.  
6 Success of the deep sclerectomy with collagen implant  
7 compared with deep sclerectomy alone -- the difference in  
8 success is not -- how do we say this? Somebody help me.

9 DR. COLEMAN: That in this clinical trial --

10 DR. SUGAR: -- was not compared with deep  
11 sclerectomy alone and the advantage of this over deep  
12 sclerectomy alone --

13 DR. ROSENTHAL: Was not demonstrated.

14 DR. WEISS: Could we say was not examined rather  
15 than not demonstrated, because that sort of is a bias?

16 DR. ROSENTHAL: Correct, sorry. Thank you.

17 DR. SUGAR: The fornix-based flaps were used in  
18 the study --

19 DR. HIGGINBOTHAM: Primarily, not exclusively.

20 DR. SUGAR: And the repeatability of the  
21 procedure, and that there is a steep learning curve. Then,  
22 we are also suggesting to the agency that they not promote  
23 the use of the term "minimally invasive" although that would  
24 not be a labeling issue. Eve?

25 DR. HIGGINBOTHAM: Mr. Chairman, I think you have

1 covered it quite well. Thank you.

2 DR. ROSENTHAL: About the reuse, you see we do not  
3 regulate the procedure but we regulate the device. So, what  
4 we will say is reuse of the device into an already existing  
5 something, or the reuse --

6 DR. SUGAR: It is not reuse.

7 DR. ROSENTHAL: You know what I mean, the use of a  
8 second device in the scleral -- whatever it is called, the  
9 space that the device kept open. To put another one in if  
10 there is ultimate failure has not been studied. But you  
11 don't want to make a comment about a second procedure using  
12 a second device elsewhere -- do you see what I am trying to  
13 say? You know, you do one superior temporally and it fails  
14 and you have to do one superior nasally -- you don't want to  
15 make a statement about that. You were talking about using  
16 another device in the primary site. Right?

17 DR. HIGGINBOTHAM: I think that was actually  
18 brought up earlier and I think that was the gist of the  
19 comment.

20 DR. WEISS: You can just say the repetition of the  
21 surgery with the device in the same site has not been  
22 studied.

23 DR. SUGAR: Other comments on labeling?

24 DR. COLEMAN: Did you mention that you might have  
25 to use goniotomy

1 DR. SUGAR: Yes.

2 DR. COLEMAN: And then, there may be a need for  
3 additional medication or medications postoperatively to have  
4 the success rates of 78-80 percent; without postoperative  
5 medications it is around 72 percent.

6 DR. SUGAR: My understanding is that the labeling  
7 would include data on medications. You know, the outcomes  
8 would include their different thresholds for success,  
9 including outcomes and the number of medications reduced  
10 from 2.2 to 0.3, or whatever, but that data would be  
11 presented in the labeling, in the physician's labeling.

12 DR. COLEMAN: I just want to make sure that they  
13 mention about the success rate though without medications,  
14 which was 72 percent at 12 months.

15 DR. SUGAR: Eve?

16 DR. HIGGINBOTHAM: Forgive me if this might be a  
17 comment taken out of order but it is something that I think  
18 would be important to actually address, and that is, I don't  
19 recall because it has been quite some time since I read the  
20 PMA, whether or not they actually dictated to the clinicians  
21 the frequency of use of postoperative steroids. Given that  
22 this is a collagen implant and the fact that this is  
23 primarily a space maintainer, I would think that we want to  
24 at least examine that issue and perhaps address or not  
25 address, depending upon what was done -- and maybe we can

1 get the sponsor to actually help us with this, to what  
2 extent we need to dictate to the clinicians how  
3 postoperative steroids should be used.

4 DR. SUGAR: In the labeling presented in our  
5 package there is no comment on postoperative management that  
6 I can see. Can the sponsor comment on that?

7 DR. BYLSMA: The initial protocol allowed steroids  
8 for up to three months postoperatively. This was in far  
9 excess of what was needed, as evidenced clinically at the  
10 slit lamp because the eyes were so very quiet. Generally,  
11 patients received one bottle of a combination antibiotic and  
12 steroid drop, one bottle they used four times a day until  
13 that was gone and that was the entire steroid regimen.

14 DR. SUGAR: So, Eve, what are you suggesting?

15 DR. HIGGINBOTHAM: Well, I guess my question is  
16 that was the way that you prescribe steroids. Was that the  
17 same use in all the other eight centers?

18 DR. BYLSMA: I don't know specifically every  
19 center but in general yes.

20 DR. HIGGINBOTHAM: So, I still remain a bit  
21 unclear on this point and I wonder if we should add a  
22 statement that states that it is unclear to what extent  
23 postoperative steroids, in terms of use or frequency of use,  
24 can actually enhance or diminish the space maintaining  
25 effects of this device.

1 DR. SUGAR: Or to say that the role of  
2 postoperative steroids in this device has not been  
3 adequately studied. This wasn't really a study and  
4 different people did different things.

5 DR. WEISS: You want to be careful though of  
6 making the clinician feel that you are not allowed to use  
7 postoperative steroids when they actually did use it in the  
8 study and had good results.

9 DR. SUGAR: So, how would you like to suggest we  
10 word it?

11 DR. WEISS: I would say that the dosage, the  
12 frequency and duration of postoperative steroids with this  
13 device and surgical procedure has not been delineated.  
14 Those were Michael's words. I think those are good ones.

15 DR. SUGAR: Is that okay with you?

16 DR. HIGGINBOTHAM: More or less.

17 DR. BRADLEY: Just some clarification, Joel. Some  
18 comment and now recommendation regarding the knowledge of  
19 the procedure's efficacy up to one year -- is that some  
20 statement going in? I am trying to remember what you said.  
21 There is a reason why I am asking this.

22 DR. SUGAR: I think that there is insufficient  
23 data after one year, as it stands right now.

24 DR. BRADLEY: Perhaps I misunderstood --

25 DR. SUGAR: We said there is no information on the

1 long-term --

2 DR. BRADLEY: That us what I thought you said,  
3 there was no information. I am recalling the sponsor  
4 presenting some evidence. It may not have been in their  
5 study. It is under a section "are there studies documenting  
6 long-term efficacy of the AquaFlow device." I am looking at  
7 a graph that goes out to 24 months. So, to say that there  
8 is no evidence is not correct, I think.

9 DR. SUGAR: Insufficient?

10 DR. BRADLEY: I am not sure you could even say  
11 that.

12 DR. SUGAR: I thought that Eve, when she put up  
13 the slides, showed the actual number of patients followed,  
14 the actual percentage of the initial cohort that was seen at  
15 12 and 24 months, and showed, you know, a marked decline.

16 DR. BRADLEY: Just to clarify, yes, and I think  
17 Eve was describing the FDA's recommended study that the  
18 sponsor perform. But as Ralph told us earlier, any evidence  
19 they bring to the table is fair enough, and I think they  
20 have this additional other study. I don't know exactly  
21 which study they are quoting. Well, there are four other  
22 studies but they did bring other data from previous studies,  
23 I presume, out to two years.

24 MS. NEWMAN: Well, the other issue though is do  
25 they have additional data for us. I mean, if they started

1 the study in '97 and went to '99, you know, do they have  
2 that information and it is just not in here? You know, you  
3 can ask them to gather that, can't you?

4 DR. SUGAR: Yes, we can ask for post-marketing.

5 DR. HIGGINBOTHAM: I wanted to address this.

6 DR. SUGAR: Go ahead.

7 DR. BRADLEY: I am not sure we have changed the  
8 wording, but perhaps I still need somebody to explain to me  
9 how we deal with this. I mean, the sponsor did present data  
10 out to 24 months. Are we saying we don't believe the data,  
11 or it is not good enough? Therefore, how do we write that  
12 into the document?

13 DR. SUGAR: I think the suggestion was that the  
14 numbers were not sufficient. Go ahead, Eve.

15 DR. HIGGINBOTHAM: I wanted to address the other  
16 data. One of the things I tried to bring out in terms of  
17 the discussion was the fact that various demographic  
18 characteristic differences can influence the outcome of the  
19 procedure. So, we can't necessarily compare an American  
20 cohort of patients to a Swiss cohort of patients -- sorry,  
21 Dr. Mermoud -- particularly if some of those patients didn't  
22 even have meds. So, there is so much variation across the  
23 board in the American population -- we do have significant  
24 differences. That is why I can't necessarily say that it is  
25 relevant. Ideally, it would have been nice if there had

1 been a case-control study at the very least at the various  
2 centers but, without that and because it wasn't asked for,  
3 we can't ask for it after the fact.

4 DR. SUGAR: Have we covered the labeling to the  
5 satisfaction of Ralph?

6 Number three, do the data presented for the  
7 AquaFlow device support reasonable assurance of safety and  
8 effectiveness for the indication as stated?

9 I think we have certainly discussed this in a sort  
10 of global sense. Is there any issue that anyone wants to  
11 add to what has already been said? If not, then I think we  
12 have carried out our discussions of the questions and the  
13 issues. Prior to our voting specifically, there is an open  
14 public hearing if anyone wants to comment, and then there  
15 are comments from the sponsor and from the agency. So, is  
16 there anyone from the public who would like to make comments  
17 to the panel? If not, would the sponsor like to come to the  
18 table and make any comments?

19 DR. ROSENTHAL: FDA first.

20 DR. SUGAR: I am sorry, FDA first.

21 DR. ROSENTHAL: My only comment is that since  
22 there have been issues relating to follow-up, could you  
23 address in your ultimate decision-making and vote whether or  
24 not you feel post-market follow-up in this group of patients  
25 in the cohort that they studied would be indicated? I would

1 like that to be addressed in your final discussion.

2 DR. SUGAR: So, you are asking us to give you our  
3 opinion on post-marketing follow, or post-approval follow-  
4 up.

5 DR. ROSENTHAL: Well, there are several voting  
6 options and I would like you to address this issue in one of  
7 those voting options, and vote on it. I need to have a  
8 sense of the panel.

9 DR. SUGAR: Okay. Dr. Higginbotham?

10 DR. HIGGINBOTHAM: I just wanted to, I guess,  
11 reaffirm my interest in having additional follow-up on these  
12 patients, and whether it is 70 percent follow-up at 2 years  
13 or 80 percent follow-up at 2 years, I think we do need to  
14 have more than just 8 percent of the original cohort.

15 DR. SUGAR: Dr. Pulido?

16 DR. PULIDO: When we go to deliberations, i would  
17 like to then ask my esteemed glaucoma colleagues what bar  
18 they would set for this device that we would at two years  
19 say this device is having problems? Because just to say,  
20 well, we are going to collect more data -- I want to know  
21 what we want to do with that data.

22 DR. ROSENTHAL: Excuse me, Dr. Pulido, but  
23 theoretically the device isn't there. So, all you could do  
24 would be to amend the labeling or amend the summary of  
25 safety and efficacy, whatever we amend, to explain what the

1 two-year follow-up is.

2 MS. NEWMAN: Well, I think it is important because  
3 if patients need to go back on medications you need to  
4 inform your consumer. I mean, it is not just the clinician;  
5 it is consumers because they invariably think some of these  
6 surgeries are for life and you are incurring costs and other  
7 things and they need to be informed. So, the thing  
8 dissolves, I agree, but the issue is what is going on with  
9 the glaucoma.

10 DR. ROSENTHAL: Yes, we would do it in the  
11 physician labeling. I don't think we are planning to have  
12 patient labeling for this device.

13 MS. NEWMAN: So, the physician should inform the  
14 consumer --

15 DR. ROSENTHAL: Absolutely.

16 MS. NEWMAN: -- prior to the surgery.

17 DR. ROSENTHAL: Absolutely.

18 DR. BANDEEN-ROCHE: I just recommend that there  
19 will also be post-marketing surveillance in a broader sample  
20 of physicians than those who comprise the current study.  
21 Maybe that is already being discussed but I wanted to at  
22 least raise it.

23 DR. ROSENTHAL: Sorry, I don't think that is the  
24 case, Dr. Bandeen-Roche. In fact, I mean, there are two  
25 ways of doing post-market evaluations. One is on the

1 existing cohort, which is generally the least burdensome  
2 approach. To ask them to begin to look at a large cohort of  
3 patients, I don't think would be the least burdensome  
4 approach to this problem and I don't think we would be able  
5 to do that.

6 DR. SUGAR: Dr. Yaross has not been heard from in  
7 this discussion. Do you have comments? I don't know, when  
8 we get to voting whether there is more discussion or not.  
9 Please?

10 DR. YAROSS: Thank you, Mr. Chairman. I think the  
11 panel has covered the concerns.

12 DR. SUGAR: Does the sponsor wish to make a  
13 closing statement?

14 MR. ZIEMBA: No, sir, we have no additional  
15 comments. Just thank you for your review.

16 DR. SUGAR: That was a brief closing remark. Now  
17 we are going to go through the formality of reviewing our  
18 voting options. Go, ahead.

19 MS. THORNTON: The Medical Device Amendments to  
20 the Federal Food, Drug and Cosmetic Act, as amended by the  
21 Safe Medical Devices Act of 1990, allows the Food and Drug  
22 Administration to obtain a recommendation from an expert  
23 advisory panel on designated medical device premarket  
24 approval applications, or PMAs, that are filed with the  
25 agency. The PMA must stand on its own merits, and your

1 recommendation must be supported by safety and effectiveness  
2 data in the application or by applicable publicly available  
3 information.

4           Safety is defined in the Act as reasonable  
5 assurance, based on valid scientific evidence, that the  
6 probably benefits to health, under conditions on intended  
7 use, outweigh any probable risks. Effectiveness is defined  
8 as reasonable assurance that in a significant portion of the  
9 population the use of the device for its intended uses and  
10 conditions of use, when labeled, will provide clinically  
11 significant results.

12           Your recommendation options for the vote are as  
13 follows. Number one, approval if there are no conditions  
14 attached. Number two, approvable with conditions. The  
15 panel may recommend that the PMA be found approvable subject  
16 to specified conditions, such as physician or patient  
17 education, labeling changes, or a further analysis of  
18 existing data. Prior to voting, all of the conditions  
19 should be discussed by the panel. Not approvable is your  
20 third option. The panel may recommend that the PMA is not  
21 approvable if the data do not provide a reasonable assurance  
22 that the device is safe, or if a reasonable assurance has  
23 not been given that the device is effective under the  
24 conditions of use prescribed, recommended or suggested in  
25 the proposed labeling.

1           Following the voting, the chair will ask each  
2 panel member to present a brief statement outlining the  
3 reasons for their vote. Thank you, Dr. Sugar.

4                           **Panel Recommendations**

5           DR. SUGAR: Thank you. I think we are now open to  
6 receive a motion from the panel or a panelist. Go ahead,  
7 Anne.

8           DR. COLEMAN: Yes, I wanted to make a motion that  
9 this PMA be approvable with conditions.

10          DR. SUGAR: Is there a second?

11          DR. PULIDO: Second.

12          DR. SUGAR: All those in favor?

13          MS. THORNTON: No, you don't have to --

14          DR. SUGAR: We don't have to vote on this? Well,  
15 we have to know whether we accept the motion. Sorry, never  
16 mind!

17          MS. THORNTON: The motion has been seconded. Now  
18 we need to go on to the conditions.

19          DR. SUGAR: Now we need to delineate the  
20 conditions, vote on each condition and then go back and vote  
21 on the main motion. Am I now correct?

22          MS. THORNTON: With all its attachments, yes.

23          DR. SUGAR: And, the agency is going to put these  
24 up in writing. Right now is the time when our task is to  
25 discuss the conditions, assuming that we would find this

1    approvable with conditions.  The first condition that we  
2    suggest is in the indications, that we modify the  
3    indications.

4               DR. BULLIMORE:  I respectfully suggest that the  
5    conditions are such that we don't need to have them written  
6    up on the screen.  We can verbalize them and vote on them  
7    one at a time.

8               DR. ROSENTHAL:  I agree.

9               DR. SUGAR:  That is fine with me.  If the agency  
10   can get the information down sufficiently, I don't disagree.  
11   Anne, would you like to restate the indications?

12              DR. COLEMAN:  You didn't want me to create the  
13   sentence?  Right?

14              DR. SUGAR:  The wording may be modified by the  
15   agency.  I mean, everything can be modified.

16              DR. PULIDO:  Excuse me, Dr. Matoba had made a  
17   suggestion that I thought was very reasonable.  She said why  
18   not approvable with conditions as discussed previously.

19              DR. SUGAR:  Apparently that is not acceptable to  
20   the agency.

21              MS. THORNTON:  No, I am sorry, we can't do that.  
22   We have to go through each condition and you vote on each  
23   one.  Then, at the end the main motion is restated with the  
24   conditions that you voted on.

25              DR. YAROSS:  Could one condition for voting be the

1 labeling recommendations as previously discussed?

2 DR. ROSENTHAL: Yes.

3 DR. SUGAR: It doesn't bother me.

4 MS. THORNTON: No, not each of the labeling  
5 recommendations but lay out the list of labeling  
6 recommendations.

7 DR. SUGAR: I think we can state the whole list  
8 and not vote on each one.

9 MS. THORNTON: So it is clear which one you are  
10 voting on.

11 DR. SUGAR: So, Anne, could you?

12 DR. COLEMAN: Let me try.

13 DR. SUGAR: Please.

14 DR. COLEMAN: The AquaFlow device is an adjunctive  
15 device that is indicated in patients with primary open-angle  
16 glaucoma, pseudoexfoliative glaucoma and pigmentary glaucoma  
17 or combined mechanism glaucoma --

18 [Chorus of "slow down"]

19 I have it written down here.

20 MS. THORNTON: Just read it a little slower.

21 DR. COLEMAN: The AquaFlow device is an adjunctive  
22 or adjunct device that is indicated in patients with primary  
23 open-angle glaucoma, pseudoexfoliative and pigmentary  
24 glaucoma or combined mechanism glaucoma with minimal  
25 peripheral anterior synechiae where intraocular pressure

1 remains uncontrolled despite maximally tolerated medical  
2 therapy, and the patients have undergone a successful  
3 concurrent deep sclerectomy and no other prior conjunctival  
4 surgery.

5 DR. SUGAR: I think that covered all of what we  
6 had in our discussion before. Now, does that need to be  
7 seconded before it is voted on? Yes? Is there a second? A  
8 modification?

9 DR. HIGGINBOTHAM: Discussion.

10 DR. SUGAR: Well, it needs to be seconded before  
11 it is discussed. Please second it.

12 DR. BULLIMORE: Second.

13 DR. SUGAR: Thank you. Go ahead.

14 DR. HIGGINBOTHAM: As I recall, one of the  
15 inclusion criteria included patients that could have at  
16 least one-twelfth of the angle closed with PAS. So, I think  
17 my suggestion would be just to say primary open-angle  
18 glaucoma because most of the patients, 90 percent of the  
19 patients were POAG.

20 DR. SUGAR: Almost 97 percent.

21 DR. HIGGINBOTHAM: Ninety-seven percent, and  
22 exclude all the secondary open-angle glaucomas and don't  
23 even get into a discussion on PAS.

24 DR. SUGAR: Do you accept that?

25 DR. COLEMAN: I accept that.

1 DR. SUGAR: So, the motion has been modified.

2 DR. ROSENTHAL: Restate it, please.

3 DR. COLEMAN: The AquaFlow device is an adjunctive  
4 device that is indicated in patients with primary open-angle  
5 glaucoma where intraocular pressures remain uncontrolled  
6 despite maximally tolerated medical therapy, and the  
7 patients have undergone a successful concurrent deep  
8 sclerectomy and no prior conjunctival surgery.

9 DR. SUGAR: So, that is the motion on the floor.  
10 Do you want to discuss the motion?

11 DR. PULIDO: My concern about that motion is that  
12 the fact that these particular patients did not have prior  
13 conjunctival surgery does not necessarily mean that this may  
14 not work for other patients that have had prior conjunctival  
15 surgery. So, therefore, I would recommend deleting that  
16 part out and putting that within the precautions.

17 DR. SUGAR: In counter to that, you know, it also  
18 wasn't tested in people with hemorrhagic glaucoma or  
19 neovascular glaucoma and so forth. So, that we state that  
20 because that is the way the study was done. None of the  
21 patients had prior conjunctival surgery. That doesn't mean  
22 a physician cannot choose to use it in other situations.  
23 Based on the data presented to us, that is supported I  
24 think, but I am not supposed to make a statement. Eve?

25 DR. HIGGINBOTHAM: Mr. Chairman, I would like to

1 speak against that comment because having previous  
2 conjunctival surgery significantly enhances the risk of  
3 failure, and we don't have any evidence that this is  
4 effective in that subgroup. So, I would like to speak  
5 against Dr. Pulido's suggestion.

6 DR. SUGAR: Okay. Can we vote on this motion?

7 All those in favor, signify by saying aye.

8 [Chorus of ayes]

9 Any opposed?

10 [One nay]

11 One opposed. Next, I would like to ask for a  
12 motion concerning labeling recommendations.

13 DR. COLEMAN: I would like to move that we accept  
14 labeling recommendations as discussed previously.

15 DR. SUGAR: I think we need to delineate them.

16 DR. SUGAR: Mark, do you have them? Go ahead.

17 DR. BULLIMORE: I move that the labeling include  
18 statements on the following: That there are limited data on  
19 effectiveness on non-Caucasians. There has been no  
20 conclusive demonstration that this adjunct device produces  
21 an end result that is any better than deep sclerectomy  
22 alone. That long-term follow-up data are limited. That  
23 secondary procedures have not been evaluated. The device  
24 has not been thoroughly evaluated in glaucomas other than  
25 POAG. That a proportion of patients will need to undergo

1 goniopuncture. That there is a steep learning curve  
2 associated with the device. If I have missed any, I will  
3 accept them as friendly amendments.

4 DR. SUGAR: Can I suggest that we also discuss  
5 that fornix-based flaps were used in the study and should be  
6 mentioned in labeling.

7 DR. BULLIMORE: Point of order, Mr. Chairman, I  
8 think someone needs to second my motion before we can have  
9 amendments.

10 DR. SUGAR: I am just telling you what to say --

11 DR. BULLIMORE: Do you want me to start again?

12 DR. SUGAR: No, that fornix-based flaps were used  
13 in a majority of patients in the study.

14 DR. BULLIMORE: My thoughts precisely.

15 DR. SUGAR: That postoperative frequency and  
16 duration of steroid use was not delineated in the study. I  
17 think those are the two that I had on my list.

18 DR. BULLIMORE: From a parliamentary point of  
19 view, it is much easier if someone seconds my motion and  
20 then you make the amendments and I accept them.

21 DR. MATOBA: I second your motion and then I have  
22 a comment. Is that okay?

23 DR. SUGAR: Yes.

24 DR. MATOBA: Well, it is regarding the wording.  
25 Your statement about the steep learning curve, that means

1 you learn it quickly. So, why do you have to put that into  
2 the labeling?

3 DR. BULLIMORE: I accept the friendly amendment  
4 and delete the word "steep."

5 DR. SUGAR: Again, this will be wordsmithed by the  
6 agency.

7 DR. ROSENTHAL: We understand the sense of the  
8 panel.

9 DR. PULIDO: In addition, not only non-Caucasian  
10 but also younger age is associated with poor outcome.

11 DR. ROSENTHAL: Excuse me, Dr. Bullimore, you were  
12 talking about limited data of effectiveness on non-  
13 Caucasians, not on the fact that it was more successful in  
14 older or younger people. So, age was not -- do you want to  
15 comment about age?

16 DR. BULLIMORE: I would like to hear some more  
17 discussion on this issue before deciding whether I accept or  
18 decline.

19 DR. WEISS: We are both saying the same thing. I  
20 think we determined that the confidence intervals for the  
21 age as well as for the sex were not strong enough to make a  
22 comment. So, I would suggest that get taken out of the  
23 labeling.

24 DR. SUGAR: I don't think we were presented with  
25 those confidence intervals. Go ahead, Karen.

1 DR. BANDEEN-ROCHE: No, indeed. I am looking at  
2 the data and in the adjusted models the confidence intervals  
3 would exclude the null. The p value is at the level of  
4 0.0288. Now, I am not a slave to p values certainly. I  
5 don't want to give that impression, but one might just state  
6 the fact that in the clinical study there was a significant  
7 association between older age and better outcomes.

8 DR. BULLIMORE: Absolutely, and the table on 591  
9 beautifully shows the p value.

10 DR. SUGAR: So, we are adding that to the list.

11 DR. BULLIMORE: I haven't accepted the amendment  
12 yet, Mr. Chairman.

13 DR. WEISS: I just have a question with that in  
14 terms of male versus female. Would you show that the  
15 confidence intervals would also indicate that you had a much  
16 better chance or success if you are male and, consequently,  
17 that should be included too?

18 DR. BANDEEN-ROCHE: Well, the strength of the  
19 evidence in terms of the precision of the estimate is less.  
20 You know, if you turn it around you certainly have not  
21 demonstrated that the efficacy is equivalent. So, it  
22 becomes a difficult issue of how to pose what you are  
23 raising.

24 DR. PULIDO: There are two tables. There is the  
25 overall success table and there is the complete success

1 table, and the p values are nicely outlined on page 591 and  
2 592.

3 DR. BANDEEN-ROCHE: Yes, I am sorry, I missed  
4 that.

5 DR. BULLIMORE: I am just trying to interpret and,  
6 unfortunately, the sponsor has rearranged the order in which  
7 the explanatory parameters appear. So, I am having  
8 difficulty just looking at one and the other.

9 DR. BRADLEY: Just a general comment. I am always  
10 concerned when we start talking about procedures being  
11 better or worse and using p values as justification. As we  
12 know, there was a large sample of males and females and it  
13 is a lot easier to identify statistically significant better  
14 or worse performance in one of those groups, but that  
15 doesn't mean that -- you can imagine the implication might  
16 be that you shouldn't do this procedure on the other group,  
17 but it may also be effective in the other group. The fact  
18 that it was slightly better in one group than another may  
19 not be pertinent to the labeling.

20 DR. BULLIMORE: What I am hearing is that the  
21 efficacy of the device may depend on the age and gender of  
22 the patient. Is that the spirit of your amendment, Dr.  
23 Pulido?

24 DR. PULIDO: Correct.

25 DR. BULLIMORE: Then I gratefully accept it.

1 DR. PULIDO: Thank you.

2 DR. HIGGINBOTHAM: I think it is in the same  
3 category as the racial issue. You just didn't have as many  
4 older patients. Forty-nine percent of the patients were over  
5 70 in this cohort. You have fewer patients I think on the  
6 lower end. So, I think I would state that there is  
7 insufficient data to confirm that there is sufficient  
8 efficacy or significant efficacy in patients that are  
9 younger -- to say there is any influence of age, gender or  
10 race. Whatever wordsmithing we use for race, I would use  
11 the same for age and gender.

12 DR. BULLIMORE: I think there are two issues here.  
13 One is whether there are sufficiently diverse populations  
14 being studied to demonstrate efficacy in the subpopulations,  
15 and that is something I introduced in my original motion  
16 with relation to race. Whether the device is more effective  
17 in subpopulations or not -- you know, we could sit here and  
18 argue all day over the p values --

19 DR. HIGGINBOTHAM: There is insufficient data. I  
20 mean, I would put it in the same category. I think it needs  
21 to be stated since the younger patients will have a greater  
22 risk of failure. So, I think just like the racial issue and  
23 conjunctival surgery issue, it needs to be stated.

24 DR. BULLIMORE: I am hearing sort of slightly  
25 conflicting things from two people I have the utmost respect

1 for.

2 DR. SUGAR: So, I think we need to discuss the  
3 amendment itself. That is, should we include in the list  
4 that data on efficacy in younger age groups is insufficient  
5 to make specific recommendations about.

6 DR. BULLIMORE: There again, I would like to hear  
7 from other panel members as well.

8 DR. SUGAR: So, we are discussing that specific  
9 amendment to your list.

10 DR. ROSENTHAL: May I make a suggestion which you  
11 may turn down, and that is, we know the issue that you are  
12 raising on age and gender -- race is another issue actually,  
13 a very important issue because we do know that it is a major  
14 factor in success of surgery --

15 DR. BULLIMORE: I am putting race in a lock box.

16 [Laughter]

17 DR. ROSENTHAL: Well, let me say that we will work  
18 with our statistician to work out the best way in which we  
19 can address race and gender in the labeling.

20 DR. BULLIMORE: And age.

21 DR. ROSENTHAL: And age.

22 DR. PULIDO: That is fine.

23 DR. COLEMAN: Also, for labeling I recommend to  
24 include about the success rate without medications and the  
25 success rate with medications because I don't see it in the

1 labeling here, and also on their table for mean intraocular  
2 pressure, I don't see where it says whether it is with or  
3 without medications. That is page 1705.

4 DR. SUGAR: So, you want to add to the list that  
5 there be specified outcome data including data on  
6 medications required.

7 DR. COLEMAN: Right, and what the success rates  
8 were with medications, and what the success rates were in  
9 individuals without medications.

10 DR. SUGAR: Could we expand that to have them list  
11 outcomes by their four different thresholds? That is,  
12 success as defined by less than or equal to 21 with or  
13 without medications, less or equal to 20 --

14 DR. COLEMAN: That would be great.

15 DR. BULLIMORE: I accept that amendment.

16 DR. SUGAR: What else? All those in favor of the  
17 labeling recommendations signify by saying aye.

18 [Chorus of ayes]

19 Anyone opposed?

20 [No response]

21 The motion carries. Are there any additional  
22 recommendations? Does someone want to make a recommendation  
23 concerning post-approval or post-marketing follow-up? No  
24 one wants to make a recommendation? Eve?

25 DR. HIGGINBOTHAM: Mr. Chairman, I would like to

1 propose for consideration by the panel that we ask for  
2 continued follow-up of the original cohort, up to two years  
3 with a minimum of at least 75 percent of the original  
4 cohort.

5 DR. SUGAR: Is there a second to that?

6 DR. COLEMAN: I second it.

7 DR. SUGAR: All right, it has been seconded. Any  
8 discussion? Go ahead, Jayne.

9 DR. WEISS: I am unclear. Let's say they only can  
10 get 60 percent, then what happens?

11 DR. HIGGINBOTHAM: Well, I guess maybe we could  
12 just state a reasonable number of patients to assure  
13 efficacy, and we will leave that up to the discretion of the  
14 FDA. Glaucoma patients do return, unlike refractory  
15 patients.

16 DR. SUGAR: Does the seconder agree with the  
17 modification?

18 DR. COLEMAN: Yes, I do.

19 DR. WEISS: That is because we can fix the  
20 refractory surgery patients.

21 [Laughter]

22 DR. SUGAR: Is there any discussion?

23 [No response]

24 So, we would like to vote on the motion concerning  
25 additional follow-up data. All those in favor, signify by

1 saying aye.

2 [Chorus of ayes]

3 Any opposed?

4 [No response]

5 Are there any additional conditions that anyone  
6 would like to suggest? If not, then we need to return to  
7 the main motion, which is that PMA P000026 be considered  
8 approvable with the conditions as stated. Is everyone ready  
9 for the main vote? If so, we can vote on the motion, which  
10 is that this PMA be considered approvable with conditions as  
11 delineated. All those in favor, signify by raising your  
12 hand.

13 [Show of hands]

14 All those opposed?

15 [One hand raised]

16 One. We now will poll the members of the panel.

17 We will start with Karen and we will include basically  
18 everybody at the table for their comments, except for Sally  
19 and Ralph.

20 DR. BANDEEN-ROCHE: I voted not to approve, not as  
21 a statement on the sponsor, not as a statement on the  
22 previous work on this device. It seems promising and I  
23 would say it is probably safe. But, for me, the data fell  
24 short of being able to testify that I am reasonably assured  
25 of safety and effective, not because of the variability

1 between physicians, which is inevitable; not because I want  
2 to dictate to physicians, which we should not; but because  
3 the limitations of the data design, the data sampling  
4 design, study design made it difficult for me to assess the  
5 extent to which the assessment of safety and efficacy  
6 provided might be inflated over what will be observed in  
7 practice.

8 DR. SUGAR: Dr. Bullimore?

9 DR. BULLIMORE: I voted in favor of the motion,  
10 however, I believe the agency should have requested or  
11 encouraged a randomized clinical trial with the comparison  
12 group representing the current standard of care, regardless  
13 of the regulatory status of devices and drugs that currently  
14 represent the standard of care, and I would encourage them  
15 to pursue that line of study in future PMAs.

16 DR. SUGAR: Anne?

17 DR. COLEMAN: I voted in favor of the motion  
18 because I felt that reasonable assurance of safety and  
19 effective had been found, although I would also like to  
20 reiterate that it would have been nice to have had a  
21 randomized clinical trial. It is too bad that the glaucoma  
22 specialists felt that trabeculectomies without  
23 antimetabolites wasn't a good control because in primary  
24 filtering procedures they do work, and we do find them as  
25 good controls in the United States.

1 DR. WEISS: I voted for approval because I think  
2 the sponsor clearly showed that the combination of the  
3 AquaFlow device and the surgical procedure was efficacious  
4 and safe.

5 DR. GRIMMETT: I voted approval with conditions  
6 because the data presented showed that the device was  
7 reasonably safe and effective.

8 DR. MATOBA: I also voted approval with conditions  
9 because I felt that the data presented did support the  
10 conclusion that the device is safe and effective.

11 DR. PULIDO: I also voted approvable with  
12 conditions. I do believe in the safety of the device. As  
13 far as the effective of the device, I still question whether  
14 it is any better than just a penetrating sclerectomy alone.

15 DR. JURKUS: I voted in favor of the motion  
16 because I believe that it was shown to be safe and  
17 effective. I was particularly impressed with the data that  
18 showed there was a decrease in the need for postoperative  
19 medications for the time studied.

20 DR. BRADLEY: I voted in favor of the proposal. I  
21 think they demonstrated it was effective and safe.

22 DR. HIGGINBOTHAM: I voted approvable with  
23 conditions. However, it is unfortunate that this was such a  
24 homogeneous group of patients in glaucoma. It would have  
25 been preferable to have greater heterogeneity, given the

1 high prevalence of glaucoma among African Americans, and I  
2 would encourage future submissions to include at least a  
3 statistical number of African Americans given the rate of  
4 blindness among those patients. So, it is unfortunate,  
5 again, that we didn't have any case-controlled studies  
6 performed here, or randomized trials, because you just  
7 cannot compare a Swiss cohort to an American cohort, and  
8 also having a stepped medical regimen would have been  
9 preferable. So, those are comments regarding clinical  
10 trials in the hopes that the FDA will take these comments to  
11 heart for future studies.

12 DR. SCOTT: I voted to recommend that this PMA be  
13 considered approvable. I think the device is safe. I think  
14 that the amendments that we suggested will be able to  
15 determine the long-term effectivity of it.

16 DR. SUGAR: I would like to have the consumer  
17 representative and industry representative make comments,  
18 please.

19 MS. NEWMAN: I agree with the panel. I just think  
20 we need more data on the cohort, more long-term data. Not  
21 being an expert in this field, it disturbs me that what is  
22 out there clinically wasn't compared to the use of an  
23 artificial device that is going to be placed in the eye  
24 whether it dissolves or not.

25 DR. YAROSS: I would only compliment the sponsor,

1 FDA staff, the panel and our new Chairman for a good  
2 discussion.

3 DR. SUGAR: This ends the discussion of this PMA.  
4 We have an issue to discuss in the afternoon, post-marketing  
5 studies for 30-day continuous wear contact lenses. We will  
6 take one hour. So, at 1:45 we will reconvene for that  
7 discussion.

8 [Whereupon, the panel adjourned at 12:45 p.m. for  
9 lunch, to reconvene at 1:50 p.m.]

## 1 AFTERNOON PROCEEDINGS

2 DR. SUGAR: We are now moving into the next issue,  
3 which is the discussion of a post-marketing approval study  
4 for 30-day continuous wear contact lenses. I guess this is  
5 going to be headed by Dr. Saviola.

6 **Post-Marketing Approval Study for 30-Day**  
7 **Continuous Wear Contact Lenses**

8 DR. SAVIOLA: Thank you, Dr. Sugar. I would like  
9 to take a moment to orient the panel for the purposes of  
10 this discussion this afternoon. Dr. Lepri will introduce  
11 the topic, and Dr. Hilmantel will actually lead the  
12 discussion.

13 At the outset, I would like to mention our  
14 appreciation for Rosalie Bright, from our Office of  
15 Surveillance and Biometrics, the Epidemiology Branch, who  
16 has helped us in some of the background work in calculations  
17 for this presentation.

18 Today we will like to hold a discussion to gather  
19 panel input in order to develop guidance for the post-  
20 approval study of extended wear contact lenses that are used  
21 beyond 7 days.

22 Although there have not been any contact lenses  
23 approved for use beyond 7 days to date, a required post-  
24 approval study is considered necessary to provide continued  
25 reasonable assurance of the safety and effective of those

1 devices if they were to be approved at a later date.

2 In the past, we have held discussions in different  
3 types of formats with the panel. Today we will be  
4 presenting a series of inter-related questions. It may not  
5 be possible to actually provide a definitive answer for some  
6 of these questions, such as who won the election --

7 [Laughter]

8 I request you consider these questions as  
9 discussion topics and provide your best opinions, both pro  
10 and con, so that we may gain a better sense of your  
11 viewpoints.

12 A final note, the reference for the safety of  
13 these devices beyond 7 days is really the literature that  
14 has been published over the last 13 or so for all extended  
15 wear lenses. You are not asked to define acceptable rates  
16 in the context of a premarket approval application, rather,  
17 you will be providing us your views in general regarding the  
18 topics for discussion. Basically, we are dealing with what  
19 we need to do to provide guidance to manufacturers.

20 I am optimistic that the assembled experts will  
21 work together to provide valuable opinions for both the FDA  
22 and the regulated industry in attendance today. There is an  
23 opportunity in the agenda for public comment after we have  
24 discussed these different topics. Thank you.

25 DR. LEPRI: We are consulting you today for your

1 opinions regarding these post-market approval studies  
2 because we have concerns about longer periods of wear and  
3 potentially increased safety risks associated with new  
4 contact lens materials potentially coming to market.

5 Corneal ulcers, of course, are our main concern,  
6 although the incidence is too low to reliably determine the  
7 risk in a reasonable PMA study. The FDA believes that the  
8 best way to address this concern is to require a post-  
9 marketing approval study of the risks posed by 30-day  
10 continuous wear lenses.

11 This discussion this afternoon will be centered  
12 around discussing the study design, the feasibility, the  
13 appropriate level of acceptable risk and the statistical  
14 powers associated with them, the timing of the studies, and  
15 the definition of endpoints and the selection of  
16 participating study sites. Our goal is to ultimately  
17 provide guidance for a study design that will be least  
18 burdensome and will provide a reasonable assurance of safety  
19 for these devices.

20 I will now turn you over to Dr. Hilmantel.

21 DR. SUGAR: One moment. Go ahead, Mark.

22 DR. BULLIMORE: Do you want us to comment as you  
23 go, or sit and listen to Gene until he has finished? What  
24 is your preference?

25 DR. LEPRI: Actually, our preference is if Dr.

1 Hilmantel could give his entire presentation, during which  
2 he will pose questions. However, at the end the questions  
3 will all be repeated, much in the same format that we  
4 present a PMA because much of this information is all  
5 interconnected and it is impossible to answer one question  
6 without the context of the entire presentation.

7 DR. HILMANTEL: This will be a discussion of post-  
8 approval marketing study for 30-day continuous wear contact  
9 lenses.

10 [Slide]

11 Before we get into the details, I want to mention  
12 that this was a group project; I am just the presenter.  
13 Drs. Lepri and Saviola, of the Division of Ophthalmic  
14 Devices, and Dr. Bright of the Office of Surveillance and  
15 Biostatistics all contributed to this.

16 [Slide]

17 New contact lens materials with much higher oxygen  
18 transmission are now available, and they may have the  
19 potential for safer continuous wear for longer periods of  
20 time.

21 [Slide]

22 The incidence of corneal ulcers is the main  
23 concern in continuous wear. About three million patients  
24 now sleep in lenses regularly. In a given year, about 7000  
25 to 8000 extended wear patients have an ulcer, and roughly an

1 equal number of daily wear patients have ulcers. About half  
2 of all ulcers are contact lens related. Contact lens  
3 wearers in general are about 80 times as likely to have  
4 microbial keratitis as non-wearers.

5 [Slide]

6 Although a serious problem, the incidence of  
7 ulcers is too low to reliably determine the risk in a  
8 reasonable PMA study. A typical PMA study may have about  
9 400 to 800 subjects in a study of 6-12 months duration.

10 I want to emphasize that we will not talk about  
11 any premarket approval studies in this discussion. We will  
12 not discuss any results from any PMA studies. All of this  
13 discussion will center on comparison to historical norms.

14 [Slide]

15 The FDA's position is that the best way to address  
16 the concern about corneal ulcers is to require a post-  
17 marketing approval study of the risk posed by 30-day  
18 continuous wear. The FDA seeks a study design that will be  
19 least burdensome to industry and will provide reasonable  
20 assurance of safety.

21 [Slide]

22 What ulcer rate should we use for the maximum  
23 acceptable risk for statistical testing? For an estimate of  
24 what to consider as an unacceptable risk we will look at  
25 what has been done in the past.

1 [Slide]

2 In 1989, Oliver Schein presented results from a  
3 case-control study. Recall that a case-control study is one  
4 in which a group of patients with contact lens-related  
5 ulcers is compared to a matched group of controls. By  
6 comparing percentages of extended wear and daily wear  
7 patients in the two groups, the relative risk of the two  
8 modes of wear can be determined. Schein used two different  
9 control groups, a population-based control group and a  
10 hospital-based control group. Here, I will focus on the  
11 population-based control, which is the middle column,  
12 because it has narrower confidence intervals.

13 This table displays how the risk was found to  
14 increase with each additional day of wear. So, if you look  
15 at the first row, patients who had slept in their lenses  
16 only one night had about 3.5 times the risk of an ulcer as  
17 daily wear patients. Patients who slept in their lenses  
18 between one night and a week had about 7 times the risk.  
19 Patients who had slept in their lenses from one week to two  
20 weeks had about 12 times the risk of daily wear. And,  
21 patients who slept in their lenses more than two weeks had  
22 about 15 times the risk of daily wear.

23 [Slide]

24 Using this data, the FDA recommended limiting  
25 continuous wear to a maximum of 7 days. From this 1989

1 Schein data, it seems that a relative risk of about 12-15  
2 compared to daily wear was considered unacceptable.

3 [Slide]

4 Eugene Poggio's 1989 study found that the  
5 incidence of ulcers was 4 per 10,000 in daily wear patients;  
6 20 per 10,000 in extended wear patients. Poggio's study  
7 included a survey of all ophthalmologists in a 5-state area.  
8 The ophthalmologists reported all new contact lens-related  
9 ulcer cases in a 4-month period.

10 [Slide]

11 Assuming that 15 times the risk of daily wear is  
12 unacceptable, this means that 60 per 10,000 is too much  
13 risk; 60 per 10,000 is about 2-4 times the risk of 7-day  
14 extended wear. Similarly, if 12 times the risk of daily  
15 wear is unacceptable, that means that 48 per 10,000 is too  
16 much risk; 48 per 10,000 is about 2.4 times the risk of 7-  
17 day extended wear.

18 [Slide]

19 Although all these rates seem quite low, we have  
20 to consider that these are annual ulcer rates. Here we  
21 display the lifetime ulcer risk as a function of the number  
22 of years a patient wears contact lenses.

23 On this graph the Y axis is the lifetime ulcer  
24 risk; the X axis is the number of years a patient is in  
25 contact lenses. The lowest line represents an annual rate

1 of 4 per 10,000, which is the current daily wear rate of  
2 ulcers. The middle line is a rate of 20 per 10,000, which  
3 is the current 7-day extended wear rate. The upper line  
4 represents a rate of 60 per 10,000 per year.

5 In my experience, it is pretty uncommon to see a  
6 patient who has been in contact lenses for 40 years, but it  
7 is not too, too uncommon to see someone who has been in  
8 contacts for 20 years. So, I want to focus on that line,  
9 the vertical line in the middle. Someone who is a daily  
10 wear patient, on the lower line, would have a lifetime rate  
11 of ulcers of 1 percent if they are in contacts for 20 years.  
12 Someone in the middle line, who is a current 7-day extended  
13 wear patient, would have a lifetime risk of about 3 percent.  
14 Someone who is in the upper line, 60 per 10,000, would have  
15 a lifetime risk of about 12 percent.

16 This is clearly something that is not desirable.  
17 Remember though that about 90 percent of ulcers are not  
18 associated with vision loss. Thus, a person on the top line  
19 would probably have a lifetime risk for some loss of vision  
20 of only about 1 percent, maybe half of that for severe  
21 vision loss.

22 [Slide]

23 What ulcer rate does the panel think we should use  
24 as the maximum acceptable risk for statistical testing? 60  
25 per 10,000, or about 3 times the 7-day extended wear rate;

1 48 per 10,000, about 2.4 times the 7-day rate; or some other  
2 rate perhaps you could suggest?

3           This maximum acceptable risk is not the ulcer rate  
4 we want the new lenses to show but an upper bound. The  
5 sample ulcer rate must be significantly below this upper  
6 bound for a decision that the lenses are safe. Now, you  
7 might want to say this is a no-brainer that you don't want  
8 any risks, so your maximum acceptable risk is just, say, 21  
9 per 10,000, just a little bit above the current rate. But  
10 if you pick that number you are going to need a sample size  
11 of, like, about 30 million. So, it is really not that  
12 simple.

13           [Slide]

14           What type of study should be recommended? A case-  
15 control study to assess relative risk, or a cohort study to  
16 determine the incidence?

17           [Slide]

18           Advantages of a case-control study are that it can  
19 assess the relative risk of different actual wearing  
20 schedules. Not everyone will be wearing lenses 30 days;  
21 some may wear them 2 weeks; some 1 week.

22           It is good for the study of rare diseases. It is  
23 relatively inexpensive because you deal with a small number  
24 of subjects. You can assess the relative risk of different  
25 hygiene practices. To me, the most important is this last

1 one, it provides a "real world" environment. Patients and  
2 practitioners are not self or other selected.

3 [Slide]

4 Some disadvantages of a case-control study are  
5 that it requires a waiting period until 30-day lenses have  
6 established sufficient market share. You cannot go out as  
7 soon as the lenses are approved and run a case-control  
8 study.

9 It only assesses the relative risk, not actual  
10 incidence of ulcers. Ulcer rates for 7-day lenses may have  
11 changed since 1989, but Cheng, in a 1999 study, found that  
12 the incidence in The Netherlands was similar to that of the  
13 1989 Poggio study. In studies the size of Schein's study, a  
14 case-control study will produce large confidence intervals.

15 [Slide]

16 Will there be difficulty in getting enough  
17 extended wear ulcers to run an effective case-control study?  
18 This is a question that we would particularly like to  
19 address to the cornea people on the panel.

20 Schein, in his 1989 study, had 86 ulcers, 52 of  
21 which were extended wear or about 8-9 from each of 6  
22 university centers in a 1-year study. Remember that half of  
23 all contact lens-related ulcers are daily wear. Thus, it is  
24 probably unrealistic to collect more than 60-120 extended  
25 ulcers in a 1-year multicenter study.

1           The third factor to consider is that there has  
2 been a change in the pattern of care for ulcers since the  
3 1980s. In the late '80s, virtually all ulcers were seen by  
4 ophthalmologists, many of them by cornea specialists.  
5 Today, many ulcers are treated by optometrists, and the  
6 availability of siloxin and occuflox mean that fewer are  
7 referred to sub-specialists.

8           [Slide]

9           When you are trying to determine the maximum  
10 acceptable risk, you need to consider the relationship  
11 between that maximum acceptable risk and the required sample  
12 size. In this table, we are trying to answer the question  
13 are 30-day lenses equally safe as 7-day lenses, or are they  
14 less safe? Each row tells the required sample size for the  
15 given assumptions. The relative risk is the risk of 30-day  
16 wear divided by the risk of 7-day wear. The last column on  
17 the right is the proportion of the control group that is 30-  
18 day wear. This is largely determined by marked penetration.  
19 For a fixed power, choosing the maximum acceptable risk  
20 determines the sensitivity of the test to deviations from a  
21 relative risk of 1. The smaller the number, the greater the  
22 sensitivity. The power in all these cases is taken to be 80  
23 percent. The control to case ratio is the number of control  
24 subjects you accumulate for each ulcer case.

25           What does this all mean? Let's take a look at the

1 bottom row here, if we want to be 80 percent confident that  
2 our test will detect a relative risk of 3, then we need a  
3 sample size of 66 ulcers. Say we want to test with greater  
4 sensitivity, let's look at the top row. If we want to be 80  
5 percent confident that our test will detect a relative risk  
6 of only 1.7, then we need a sample size of 298 ulcer cases.  
7 To get a greater sensitivity you must have a larger sample  
8 size. The larger sample sizes shown here are not practical.  
9 They are just put up for illustrative purposes.

10 [Slide]

11 Statistical power is a key measure of our  
12 confidence in product safety. Power and sample size are  
13 strongly related. In most studies in which we are trying to  
14 show superior efficacy, using the conventional alpha level  
15 of 0.05 ensures that we will make a mistake only 5 percent  
16 of the time. With this type of experimental design, our  
17 confidence in the safety of the device is determined by the  
18 power. Although using a power of 80 percent is fairly  
19 conventional, in order for the FDA to have confidence in the  
20 safety of the lenses we might want to use a power of 90  
21 percent or higher.

22 In this table we are holding the sensitivity and  
23 market penetration constant and showing how increasing the  
24 power makes the sample size requirements go up. Remember  
25 that 1 minus the power is the probability that our test will

1 be incorrect when it says that the lenses are safe. Let's  
2 look at the bottom row now for particulars. What does this  
3 mean? If the true relative risk is 3 with a sample size of  
4 66, our test will incorrectly declare that the lenses are  
5 equally safe 20 percent of the time. Let's go up to the top  
6 row. If we want greater confidence in our results, by  
7 upping the sample size to 111, our test will make a mistake  
8 in assessing safety only 5 percent of the time.

9 [Slide]

10 There is an interplay between market penetration  
11 and sensitivity and power of the test. Here we hold  
12 constant the number of ulcer cases and show how the  
13 sensitivity of the test improves with greater market  
14 penetration. Another way that we can achieve greater power  
15 and sensitivity is by accumulating more ulcer cases over a  
16 longer period of time. For example, the study could be run  
17 over a 2-year period instead of just a 1-year period.

18 But, again, looking at this table, you can see  
19 that as the market penetration increases you are able to  
20 test with a smaller maximum acceptable risk. But my second  
21 point is, say that you could only get 40 ulcers in a year  
22 all these studies would be impractical. But if you are  
23 willing to run the study over a 2-year period you can easily  
24 run any of these studies.

25 [Slide]

1           What statistical power would the panel recommend  
2 to ensure confidence in the result? Should we wait for  
3 greater penetration in the market in order to achieve  
4 greater sensitivity and power and run a longer study? In  
5 other words, how will you balance the benefits of getting a  
6 quick answer to those of getting a more precise answer?

7           This is a little bit like the dilemma that the  
8 networks had last night in their exit polling. All the  
9 networks wanted to be the first ones out with their  
10 projection so they had to decide is it more important to get  
11 the answer out soon, or should we wait and get a more  
12 precise answer? So, the FDA obviously doesn't want to wait  
13 10 or 15 years to find out the answer. We want to have a  
14 timely answer but we also want to have an accurate answer.  
15 We don't want to have to retract our projections.

16           By the way, there is a recent report that I just  
17 heard on the radio that the results are in from Florida, and  
18 that Mark Bullimore has won the election there.

19           [Laughter]

20           [Slide]

21           Following a cohort of 30-day wear is an  
22 alternative way to assess risk. This could be done by  
23 requiring a large number of practitioners to fill out a  
24 small follow-up questionnaire after one year of experience  
25 with the lens.

1 [Slide]

2 Some advantages of a cohort study are that it may  
3 yield quick results. We could probably have the sponsor  
4 start doing the study shortly after FDA approval. It can  
5 assess the actual incidence of ulcers, and it may be able to  
6 assess the incidence of other complications, such as corneal  
7 infiltrates and corneal neovascularization.

8 Some disadvantages of a cohort study are that you  
9 have selected patients. Patients will be self-selected.  
10 They will not be truly representative of the whole  
11 population of potential wearers. Also, not all  
12 practitioners will choose to participate in the study or be  
13 chosen by the manufacturer. Those that do participate may  
14 give a different level of care or have patients with an  
15 unusual profile.

16 These first two points are problems that we have  
17 in basically all our PMA studies. We don't really know what  
18 kind of problems we are going to run into when we are out in  
19 the real world. You also have a relatively controlled  
20 follow-up environment with this type of a study. And, the  
21 cost may be higher because of the large number of subjects  
22 that are involved.

23 [Slide]

24 Significant increases in ulcer rate are detectable  
25 with a large sample size. Here we are testing null

1 hypothesis that the ulcer rate is 20 per 10,000. In the  
2 third column a rate of 40 per 10,000, which is the third one  
3 down, corresponds to a relative risk of 2. A rate of 30 per  
4 10,000, which is either of the first two there, corresponds  
5 to a relative risk of 1.5 compared to 7-day wear.

6           Again, this table shows how the maximum acceptable  
7 risk influences the sample size. The top row shows that if  
8 we require a very sensitive test with high power, we must  
9 use an extremely large sample size. The second column in  
10 the table shows the sample ulcer rate that causes a  
11 rejection of the null hypothesis.

12           This table clearly shows that for the test to say  
13 that 30-day lenses are safe the ulcer rate of the sample  
14 must be well below the maximum acceptable risk. So, when  
15 you are choosing a maximum acceptable risk, just keep that  
16 in mind. The sample rate must be well below that.

17           [Slide]

18           What type of colleague setting does the panel  
19 recommend for implementation of a post-approval cohort  
20 study? Theoretically, a random selection will give the best  
21 estimate of the incidence. However, some of the settings  
22 will be conducive to better patient follow-up and higher  
23 percentages of patients remaining in the study.

24           [Slide]

25           Would the panel recommend a case-control study, a

1 cohort study or both? Of course, the two types of study are  
2 not mutually exclusive. It might be very attractive to  
3 require a cohort study immediately upon the marketing of the  
4 lenses and later require a case-control study after, say, 30  
5 percent market penetration has been achieved. This  
6 combination would have the advantage of getting quick  
7 results from the cohort study and verifying the safety in a  
8 non-selected population through a case-control study.

9 [Slide]

10 How would the panel define the endpoints that we  
11 are interested in for the study? This may seem like a  
12 trivial question but in past studies it has been a big  
13 problem to get clinicians to be consistent in their  
14 diagnoses. Perhaps requiring more objective criteria, such  
15 as scarring or vision loss, would clarify the results of the  
16 study.

17 [Slide]

18 We have talked about some key aspects of study  
19 design. I think it is clear from this discussion that there  
20 is a natural tradeoff between assurance of safety and study  
21 feasibility. We need to strike the right balance.

22 Thank you for your attention. Please feel free to  
23 ask any questions that you may have. I also want to point  
24 out that you have been given a handout that shows various  
25 sample sizes and how the sample size depends on the power

1 and the maximum acceptable risk levels. I think you handout  
2 has a mislabeling there because I labeled one of the items  
3 the alternate hypothesis risk rate, and I thought that was  
4 too technical. I wanted to change that to maximum  
5 acceptable risk. Are there any questions at this time?

6 DR. SUGAR: Go ahead.

7 DR. BRADLEY: I have lots of questions. Really,  
8 first the questions relate to my own ignorance in  
9 statistics. I am just remembering something I learned a  
10 long time ago about Baye's theorem, and one of the claims  
11 you made with the case study when you talked about the  
12 disadvantages is that it doesn't give you absolute risk, and  
13 in recalling Baye's theorem, if you know the conditional  
14 probabilities, one way round, you can somehow figure out --  
15 so if we know the conditional probability from the case  
16 study you know the probability that they were extended wear  
17 users, given that they have an ulcer, and what you are  
18 trying to find is the probability they have an ulcer given  
19 they are extended wear patients. And doesn't Baye's theorem  
20 allow you to do that?

21 DR. BANDEEN-ROCHE: Yes, you are correct, in my  
22 estimation, that if you have good estimates, in this case,  
23 of the population incidence in one group or the other and  
24 good estimate of the relative risk, then you should be able  
25 to calculate the incidence in the group that you are

1 interested in. Of course, that highly depends on the  
2 quality of those two separate pieces. So, both pieces that  
3 feed into Baye's formula have to be well and validly  
4 estimated.

5 DR. BRADLEY: So, I guess given the qualified  
6 confirmation, one of the shortcomings of the case study  
7 approach might not really be there. Is that correct? Mark  
8 is shaking his head.

9 DR. HILMANTEL: The trouble is every time you make  
10 an assumption it adds greater uncertainty to your results.  
11 So, you are piling uncertainty on top of another uncertainty  
12 and get less reliable results.

13 DR. BRADLEY: Okay. So, that was my first  
14 statistical type of question. The second one was regarding  
15 your slide --

16 DR. BRIGHT: Can I add something to that?

17 DR. BRADLEY: Yes?

18 DR. BRIGHT: If you do a case-control study in an  
19 environment where you know what the population is and, say,  
20 you are picking up all the cases in the population or you  
21 know what proportion of all the cases you are picking up,  
22 then you can infer the incidence rates. But if you don't  
23 really know what is going on in your population, then Baye's  
24 theory doesn't really help because you don't have all the  
25 pieces you need.

1 DR. BRADLEY: Okay. The second one is the graph  
2 you provided us with where you showed the projection of the  
3 lifetime ulcer risk, which I thought in some cases was  
4 extremely alarming where the one-year ulcer rate was 60 per  
5 10,000, which is a very high rate, I am assuming that that  
6 projection or prediction makes an assumption that everybody  
7 is equal. There is an equal chance of anybody getting an  
8 ulcer, and I just wonder whether that is really true, or  
9 whether the people who got the ulcers in the first year,  
10 they were somehow predisposed to getting ulcers and the  
11 people who did not get the ulcer in the first year somehow -  
12 - whatever it was, their immune system or whatever,  
13 predisposes them to not get ulcers. So, I wonder if you can  
14 actually make that projection to multiple use.

15 DR. HILMANTEL: Yes, I don't think there is any  
16 real evidence on that one way or the other. So, yes, it is  
17 just a straight mathematical projection.

18 DR. BULLIMORE: You could come up with a more  
19 sophisticated model. I mean, Arthur I think is right.  
20 There may be people who, by nature of their behavior -- like  
21 they are very sloppy about the way they care about their  
22 lenses, or they may have other predisposing risk factors or  
23 factors that increase their likelihood -- and you could have  
24 a high risk and a low risk population but you are still back  
25 to square one.

1 DR. BRADLEY: Well, I think basically this is a  
2 worst-case scenario, it seems to me, what you have projected  
3 there in the 20-year projections. That is, everybody is  
4 equally likely to get this.

5 DR. HILMANTEL: Yes, that is the assumption, but  
6 to address Mark's comment, Schein's study found that hygiene  
7 practices are relatively unimportant in the risk of an  
8 ulcer. They couldn't really identify any factor -- there  
9 were some minor hygiene factors but not major. Smoking was  
10 a minor factor so patients who smoke are more likely to get  
11 an ulcer. But by far the most important factor was whether  
12 someone slept in their contacts and how many days  
13 continuously they sleep in their lenses.

14 DR. BULLIMORE: Mr. Chairman, I didn't want to  
15 imply that care was, indeed, a significant factor. It is  
16 just one of the things that you could consider. So, I just  
17 want to clarify that.

18 DR. BRIGHT: Also, the numbers of people who would  
19 get the ulcer are so small they wouldn't really affect the  
20 curve much even if you took that into account.

21 DR. SUGAR: I think that this isn't necessarily a  
22 worst-case projection because you could also postulate that  
23 people who are going to wear lenses for 30 days are going to  
24 be more likely to not follow protocol and discard their  
25 lenses after 30 days and wear them even longer because, you

1 know, if they can wear them for 30 days, why not 60? That  
2 is already true for 7-day wearers. This is all a  
3 mathematical postulation, not data based, other than  
4 Poggio's and Schein's data. Dr. Scott?

5 DR. SCOTT: That, and the other thing is that  
6 people who wear their lenses for 20 years are also 20 years  
7 older, and the eye of a 20-year older person is different.  
8 There is probably decreased tear secretion. I mean, you  
9 can't project out that far. We just don't have the data.

10 DR. SUGAR: I think we are going to have this  
11 questioning with you and then we are going to need to go  
12 through each question step by step. I would prefer you  
13 would stay at the table and participate in the discussion.  
14 Go ahead.

15 DR. BRADLEY: A non-statistical question, you gave  
16 us data on the 7-day extended wear risks from -- I am not  
17 sure which study. Essentially, we had 4 in 10,000 for the  
18 daily wear contact lens wearers and it went up to -- I have  
19 forgotten the exact number but up some amount -- was it up  
20 to 20? And, the FDA apparently had approved that as being  
21 an acceptable risk. Is that correct? That was the  
22 implication I had. So, if that has been the acceptable risk  
23 already approved by the FDA, does that imply that that  
24 should be some risk that we should now tolerate for the  
25 extended wear?

1           The reason I ask that question is that in the very  
2 early statements you made the point that lens materials are  
3 improving, and all of these risks may be declining -- the  
4 daily wear risk, the 7-day risk and potentially the extended  
5 wear risk. I wonder if the extended wear risk with the new  
6 materials may drop, or have already dropped, to a level  
7 below what the FDA has already said is acceptable for the  
8 old 7-day wear lenses. Does that make any sense to anybody?

9           DR. HILMANTEL: Yes, it makes sense but the fact  
10 is that current lenses on the market basically are the same  
11 materials, by and large, as the lenses that were around in  
12 the 1980s.

13           DR. SUGAR: But the lenses being proposed are  
14 higher DK lenses.

15           DR. HILMANTEL: That is correct. Yes, we don't  
16 know the rates yet for those lenses if they are worn as 7-  
17 day lenses. We just don't know if the rate is lower.

18           DR. BULLIMORE: I have a related question. So,  
19 what you are saying is that for your comparison group you  
20 want to use 7-day extended wear. You don't want to use  
21 daily wear as your comparison group for any of these  
22 studies.

23           DR. HILMANTEL: Well, I think as a practical  
24 matter, these 7-day lenses are out there and sort of in fact  
25 we are accepting the risk that they have.

1 DR. BULLIMORE: That is fine. My next question is  
2 when you conduct these studies, be they cohort or case-  
3 control, your 7-day comparison group -- are you going to  
4 have that 7-day wear with the new materials or 7-day wear  
5 with existing materials?

6 DR. HILMANTEL: No, that would be in comparison to  
7 the existing materials. In other words, we are trying to  
8 say let's assume that the risk with current lens materials  
9 and current wearing schedules is acceptable, and we want to  
10 make sure that the new lenses that are available for 30-day  
11 wear don't pose any more of a risk than the lenses that are  
12 already out there.

13 DR. SUGAR: Let's try to go through this question  
14 by question. Obviously, there is not a right answer, A, B  
15 or C, and we are not going to be able to actually vote but I  
16 think you want to get a sense of what we feel about these.

17 So, question one is what ulcer rate does the panel  
18 think we should use as a maximum acceptable risk for  
19 statistical purposes? This is 3 times, 2.4 times or  
20 something else times the now apparently accepted rate of 20  
21 per 10,000 for 7-day extended wearers. So, 3 times would be  
22 60; 2.4 times would be 48 ulcers per 10,000 patients per  
23 year.

24 DR. BULLIMORE: I am going to ask the same  
25 question again but in the context of the FDA's question.

1 What you are proposing to do is to compare new materials 30-  
2 day wear against old materials 7-day wear. Okay? Now, you  
3 have established, based on historical precedent, that the  
4 risk associated with 30-day old materials was unacceptable  
5 but the risk associated with 7-day wear old materials was  
6 acceptable. Correct?

7 DR. HILMANTEL: Yes.

8 DR. BULLIMORE: Well, that is the benchmark you  
9 have given us.

10 DR. LEPRI: That is the benchmark that is given,  
11 and that was based on what the panel decided.

12 DR. BULLIMORE: And, in an ideal world we would  
13 say, okay, let's accept that 7-day existing material risk,  
14 and if we are going to introduce a new material it should  
15 have the same risk, not 2 times, not 3 times; it should be  
16 the same. But the problem is from a statistical point of  
17 view and determining sample size characteristics, that  
18 presents you with the problem which may be very difficult to  
19 address. You are trying to demonstrate equivalence, which  
20 is very different from demonstrating or establishing an  
21 increased risk.

22 My question again is why do you choose 7-day  
23 extended wear as your comparison group, because if you were  
24 to say, all right, we want to have the new 30-day wear of  
25 the new materials, that is what we are interested in, but we

1 want to establish that they have no greater risk than the  
2 existing ones, well, then if you reference it back to daily  
3 wear --

4 DR. LEPRI: It is almost always going to be worse.

5 DR. BULLIMORE: It is always going to be worse,  
6 but you may have an alternative approach to the one that you  
7 are proposing here. Do you see what I am saying?

8 DR. LEPRI: I understand what you are saying. I  
9 think we all understand what you are saying, that the new  
10 lens materials, if you are going to say they are equivalent  
11 statistically and every way, it is determining something  
12 different than saying something is worse in that rate, and  
13 the 7-day rates that we have now, based on these old  
14 materials, are from what was when 30-day wear was cut back  
15 to 7-day wear in the 80's when the reports of ulcers were  
16 coming in and were considered to be too high. But I think  
17 that is something we should really take into consideration,  
18 and perhaps there need to be two groups that should be  
19 considered, daily wear and the existing 7-day wear, and  
20 compare the rates of those. I don't know if that is a  
21 solution.

22 DR. YAROSS: I would like to comment on Dr.  
23 Bullimore's comment. I think you are stating the assumption  
24 that the risk with the 7-day is the maximally tolerated  
25 risk. I actually thought that was the question being put in

1 front of the panel, is that the maximally tolerated risk?  
2 Because I think there are times when greater risk is  
3 acceptable because we are always looking at a risk/benefit  
4 ratio. So, I think it is fair to put in front of the panel  
5 the question about are there benefits associated with the  
6 longer-wearing schedule that would tolerate a greater degree  
7 of risk, and if so, what?

8 DR. HILMANTEL: I don't think that is really the  
9 point that we are trying to make here. We are trying to say  
10 we don't want to really accept greater risk than what is  
11 already out there but, due to statistical uncertainty, we  
12 have to have some kind of upper bound that is higher than  
13 the current risk. We can't say, okay, prove with your new  
14 lenses that beyond a shadow of a doubt you have no higher  
15 rate than 20 per 10,000. We have to accept some kind of  
16 upper bound. If you want to think of it as a confidence  
17 interval, we have to have an upper bound to the confidence  
18 interval that is always going to be higher than the actual  
19 mean rate.

20 DR. YAROSS: Are you saying that because this is a  
21 510(k) device, or are these PMA devices?

22 DR. HILMANTEL: No, these are PMA devices.

23 DR. YAROSS: So, therefore, it really isn't  
24 formally a question of substantial equivalence but I think  
25 risk/benefit ratio does come into play.

1 DR. HILMANTEL: That is true, but I think as a  
2 practical matter it is hard to keep something off the market  
3 that is equally safe as something that is already out on the  
4 market.

5 DR. SCOTT: I don't think the real question has  
6 been asked, and that is what are the upper bounds of  
7 acceptability for 7-day wear. You used the term  
8 "benchmark." Well, it is not a benchmark; it is "what is"  
9 and we have said that is within the upper limits of  
10 tolerance but we haven't established the upper limits. That  
11 question probably has to be asked and answered also. I  
12 think it is the same answer. In my mind, the difference in  
13 a convenience device, which is probably somewhat a  
14 pejorative way of stating it but the difference between a 7-  
15 day interval between removal and a 30-day interval between  
16 removal doesn't make this an orphan device. So, I don't  
17 think we have to change the standards to do that, but we do  
18 have to establish what is the upper limit that we would  
19 accept for a 7-day interval lens.

20 DR. SUGAR: Go ahead, Arthur.

21 DR. BRADLEY: I think I am a bit more confused  
22 than I was a few minutes ago. You presented two options,  
23 the case-control study being one, and under the  
24 disadvantages you say it only assesses relative risk and not  
25 actual incidence. I assume by relative risk, it would be

1 relative to 7-day or daily wear. I guess I am going back to  
2 the point Mark was making, that is, we have developed this -  
3 - I hate to say benchmark but some sort of standard at the  
4 moment for what is acceptable. But that is based upon old  
5 materials. So, in the future when studies are done,  
6 presumably all the 7-day wearers will be wearing the new  
7 material lenses too. So, therefore, how would you ever --

8 DR. HILMANTEL: I don't think that is true.

9 DR. BRADLEY: -- find the incidence relative to  
10 your benchmark.

11 DR. HILMANTEL: No, that is not true. Actually,  
12 some of these newer materials are actually on the market at  
13 this time but they don't represent a significant proportion  
14 of the 7-day wear market. At least one has been approved  
15 for up to 7-day wear.

16 DR. BRADLEY: Does that point make any sense, the  
17 concern that you have a moving benchmark as the new  
18 materials change?

19 DR. SAVIOLA: I just want to comment on two  
20 things. The first what we defined back in 1989 as being  
21 acceptable, and you have to go back to the slide regarding  
22 relative risk where they broke down the number of days of  
23 wear. It is on page 3 of the handout. Again, it is not  
24 saying what the incidence rate was exactly, but in that  
25 breakdown of 1 day, 2-7 days, 8-14 days you are seeing a

1 relative risk of somewhere between 6 and 10 depending on the  
2 population you are looking at. So, that is really where we  
3 kind of set the mark at the time.

4 Now, as I am understanding Mark's comments, we  
5 have proposed this model for discussion based on comparing  
6 the new materials at 30 days to the old materials at 7 days,  
7 yet, I guess you are suggesting that perhaps we should  
8 remodel this and compare the new materials at 30 days back  
9 to daily-wear lenses because, in a sense, that is what we  
10 actually have as a reference from historical data. Is that  
11 what you are suggesting?

12 DR. BULLIMORE: Yes.

13 DR. SAVIOLA: Again, it is just a different set of  
14 calculations and different outcomes, but to get back to the  
15 question we are trying to get a sense for, the way we  
16 suggested the model using 7 days as a comparator, that is  
17 where we need to have that upper bound. If we go back and  
18 remodel this based on daily wear, then you are saying, well,  
19 the upper bound should be where it is right now. Is that  
20 your point?

21 DR. BULLIMORE: Well, I am not sure what I am  
22 saying but I understand it better now you have explained it  
23 back to me.

24 [Laughter]

25 I mean, at the end of the day you want to have

1 established what the risk of infection is with these new  
2 lenses, and whether you are going to reference that to 7-day  
3 wear of another lens, or daily wear of another lens, that is  
4 useful information that will help you, the industry, the  
5 doctors and the patients make an informed decision about  
6 what they do. Okay?

7           The reason I raise the issue is that if you are  
8 going to do any sort of study, particularly a case-control  
9 study, and you are going to invest the energy in doing that,  
10 restricting yourself to ulcers caused by extended wear  
11 lenses may be a little near-sighted and I would encourage  
12 you, if you ophthalmology for that approach and I think you  
13 will at least as one of your approaches, to make your cases  
14 contact lens related ulcers, whatever that may mean, rather  
15 than just extended wear lens ulcers. I think you will have  
16 the ability to collect more data and more useful data that  
17 way for very little more effort.

18           DR. SAVIOLA: Although the point is well taken,  
19 the reason we modeled this on 7 days is because in a  
20 premarket approval arena that really is what we are running  
21 as control lenses and it is really what we are comparing  
22 against. So, we just took the next step and used that as a  
23 model for the post-market arena. But, again, if the sense  
24 is that perhaps we should reconsider that -- I mean, this is  
25 really all amorphous at this point and we are trying to get

1 your best thoughts and opinion. So, going back and modeling  
2 it back to single use might be appropriate.

3 DR. WEISS: I would be in agreement with Dr.  
4 Bullimore because my concern would be if we are going to be  
5 comparing apples and oranges, a different lens material at 7  
6 days to a new lens material at 30 days, my feeling is the  
7 panel at that point will be asking, well, how do you know it  
8 is not the lens material versus the schedule. Then, the  
9 sponsor is going to be in the same sort of situation as they  
10 frequently are. So, what I would like to do is compare  
11 apples and apples, and if you have a new lens material and  
12 you determine what the daily wear ulcer rate is, what the 7-  
13 day wear ulcer rate is, and what the extended wear ulcer  
14 rate is, perhaps the ulcer rate for the extended wear will  
15 be similar to what it is for the 7-day wear of the old  
16 material, but if you compare it to the 7-day for the new  
17 material it may still be unacceptably high. In other words,  
18 maybe our stringency rate will get higher and as new  
19 materials come out maybe we are going to demand a lower  
20 ulcer rate. So, we shouldn't be comparing it to the same  
21 material.

22 DR. SUGAR: A quick answer to Dr. Scott's  
23 question, in Poggio's study, from which the 20 per 10,000  
24 comes, the 95 percent confidence interval for extended wear  
25 soft lenses was between 15 and 27. So, it was still

1 relatively tight and didn't approach these numbers.

2 DR. BANDEEN-ROCHE: Three points. First, I wanted  
3 to follow-up on the risk/benefit comment. I thought a lot  
4 about this when I read through these slides, and please  
5 correct me if I am wrong but it seemed that for the vast  
6 majority of people the added benefit is pretty minor of  
7 being able to take out your contact lenses once every four  
8 weeks as opposed to once every week. So, if that is true,  
9 then risk should be held to a comparably high standard.

10 The second point is that in terms of what you have  
11 there, what we should use as a maximum acceptable risk, I  
12 agree ideally with what Dr. Scott was saying. That seems  
13 like the ideal approach to decide what is an appropriate  
14 standard. I realize that may not be feasible but I just  
15 wanted to voice my agreement.

16 Finally, in terms of the maximum acceptable risk  
17 and risk/benefit ratio, that will certainly vary for  
18 different people probably, and I agree with Dr. Bullimore  
19 that what we really need to do is to precisely estimate what  
20 the risk is. So, in terms of design aspects, we wouldn't  
21 only be thinking about power but the precision with which we  
22 are estimating the risk.

23 MS. NEWMAN: A benefit you didn't mention is cost.  
24 If you don't have to take out these contact lens for 30  
25 days, that is a big benefit to consumers.

1 DR. JURKUS: Also another benefit would be in  
2 relation to the refractive surgery patient and that people  
3 may consider doing extended wear for 30 days not having to  
4 handle their lenses and mess them up, as opposed to having  
5 refractive surgery done. So, on your initial statement I  
6 would tend to disagree with you.

7 DR. BANDEEN-ROCHE: That is very useful, thank  
8 you.

9 DR. SCOTT: When you were talking earlier about  
10 comparing the same materials so that you could measure  
11 apples and apples and apples, because actually you are  
12 talking about a 1-day, 7-day and 30-day comparison of the  
13 same material, some of the materials don't hold up to daily  
14 wear. Putting them in and taking them out, the lenses fall  
15 apart. So, I think the concept of having a 7-day versus a  
16 30-day, from a scientific standpoint, is a valid one. But,  
17 again, when we start dividing the group in two it is going  
18 to take twice as long, or we will have to have cohorts twice  
19 as large to get the same information.

20 DR. WEISS: I think your point is very well taken.  
21 So, depending on the lens material you might not be able to  
22 have the luxury of all three groups. But I think still an  
23 apple and an apple would be better than an apple and an  
24 orange.

25 The other thing was in terms of the comment about

1 the advantage or subjective assessment of whether extended  
2 wear is worth the risk, there are also elderly patients who  
3 are incapable of taking their lenses in and out, and for  
4 those patients extended wear is really the only choice if  
5 they are going to be wearing contacts.

6 DR. BULLIMORE: Just a point of clarification, I  
7 was not proposing a cohort study where you have 1-day, 7-  
8 day, 30-day patients with different lenses. Okay? I was  
9 putting it in the context of a case-control study where you  
10 collect cases, wait for cases to come in with contact  
11 related ulcers and you see what the practitioners are doing  
12 rather than programming your cohort accordingly in the  
13 beginning.

14 DR. SUGAR: Do you have a sense of the feeling of  
15 the panel?

16 DR. HILMANTEL: I just wanted to respond to Mark's  
17 last point here. That is one of the advantages of a case-  
18 control study, that you can assess the different wearing  
19 schedules. Some people will be wearing their lenses just  
20 one or two days; some people a week; some people two weeks.  
21 You can assess the risk involved in different wearing  
22 schedules.

23 DR. SUGAR: The sense of the panel that I am  
24 getting is that the benchmarks proposed, even though they  
25 are not proposed as benchmarks but the upper confidence

1 level limits are higher than we would consider acceptable.  
2 No? Okay, then we have to correct that. The other was that  
3 -- I just lost my trend -- that the acceptable level now for  
4 7-day wear may not be actually a contemporary appropriate  
5 level with newer technologies. Is that wrong?

6 DR. PULIDO: I would say that Gene made a very  
7 cogent argument for the fact that the levels now for 7-day,  
8 the lifetime ulcer risk is low enough that that is a  
9 reasonable measure. So, why can't we use that as the  
10 standard to measure the others against?

11 DR. SUGAR: That is what I was saying, that 3  
12 times that or 2.4 times that is not an acceptable level. I  
13 am not talking about statistics; I am talking about clinical  
14 practice.

15 DR. BULLIMORE: Well, but in designing a study and  
16 some of the numbers that Gene gave, I mean, basically you  
17 are coming up with a number of patients you need to  
18 demonstrate 2 or 3 times difference. So, what you may end  
19 up doing is demonstrating statistical equivalence because  
20 when you actually do the study you fail to find a 2 times or  
21 a 3 times rate.

22 Let's take a scenario, let's say we say we are  
23 happy to accept the relative risk, or we want to find the  
24 relative risk of 3 and design a study to do that, what we  
25 are saying is that we will accept anything less than 3 as

1 being statistically equivalent to 1 because we won't have  
2 the statistical power to find those differences, the smaller  
3 relative risks, given the constraints of the study design.  
4 So, we need to think about it in those terms.

5           So, rather than thinking about what is maximally  
6 acceptable, you need to think about what is clinically  
7 equivalent. So if, for example, you know or you accept at  
8 the moment that the relative risk of extended wear, relative  
9 to daily wear, is, say, 7 times; 7-day relative to daily  
10 wear is 7 times, if it was 14 times, i.e., if 30-day wear  
11 was 14 times more risky than daily wear, i.e., 2 times 7-day  
12 wear, you would consider the 7 and the 14 equivalent. I  
13 mean, that is really I think what we are being asked here.

14           DR. SUGAR: I am not sure. I think that you would  
15 demonstrate -- in terms of projecting a population that you  
16 would need to study to show within those bounds equivalence,  
17 yes, that is true. And, we are talking about two different  
18 things I think in terms of acceptable for a study and  
19 acceptable for clinical practice. I think those are two  
20 different things. Karen, you maybe understand this better  
21 than I.

22           DR. BANDEEN-ROCHE: Yes, I would like to ask Dr.  
23 Bullimore if I understand what he is saying, and I would  
24 also like to thank the other panelists for correcting my  
25 view of risk/benefit. That was very enlightening.

1           Are you suggesting turning the null hypothesis  
2 around? In other words, the null hypothesis is that you  
3 have an unacceptable rate and the aim of the study is to  
4 provide positive evidence that the risk is lower than that  
5 rate, rather than the other way around which is how it is  
6 currently framed, to assume that the risk is the same --

7           DR. BULLIMORE: Not lower but not different.

8           DR. BANDEEN-ROCHE: Right. So, that would be a  
9 formal equivalence design that you are talking about.

10          DR. BULLIMORE: Yes. I will throw that back to  
11 the agency. What do you want to find? Do you want to  
12 demonstrate equivalence? Do you want to come out with a  
13 statement that with these new materials 30-day wear poses no  
14 additional risk, over and above what you would expect with  
15 7-day wear with the previous materials?

16          DR. SAVIOLA: Ideally, yes. That would be  
17 desirable.

18          DR. BULLIMORE: Because that is important to know.

19          DR. SAVIOLA: Because, again, that is what is on  
20 the market. That is what has been found to be reasonably  
21 safe and effective, no matter what the rate is considered to  
22 be.

23          DR. BULLIMORE: So, to rephrase the question to  
24 the panel, I mean, is that a reasonable goal, or are we  
25 willing to accept greater risk with these 30-day lenses

1 because of the potential benefit?

2 DR. SAVIOLA: The acceptance of greater risk is  
3 basically, as it is parenthetically stated, for statistical  
4 testing. I think in concept we all agree that there  
5 shouldn't be any more higher level at 30 days than there is  
6 at 7 days.

7 DR. BRADLEY: Boy, I am getting deeper in a hole  
8 here, I can tell you. I am having trouble with two things.  
9 I am going back and forth here. One, I am thinking from the  
10 patient's point of view what is tolerable risk. We are  
11 essentially talking about the incidence of these ulcers.  
12 That is what we talk about when we are talking about risk.  
13 And, now we are talking about statistical values of relative  
14 risk from the FDA's point of view. You know, what number  
15 should we come up with that allows the FDA to, let's say,  
16 judge whether something is equivalent or not. I am just  
17 having trouble between the sort of statistical argument on  
18 the one side, and the concern I have for the patient on the  
19 other side. Are these the same things or are they two  
20 separate entities?

21 DR. BRIGHT: Well, it makes a difference if  
22 clinically you are going to ask that the new lenses present  
23 the same risk as the old lenses. That is different from  
24 saying, okay, there is a greater benefit so greater risk  
25 will also be acceptable. Once you have resolved which way

1 you are going to go with that, then the statistical  
2 questions follow. So, I think it makes better scientific  
3 sense to resolve the clinical view of what the question  
4 should be and then figure out how to address it  
5 statistically.

6 DR. BRADLEY: I agree.

7 DR. SCOTT: I will ask a hanging question just to  
8 make a point, and then I will answer a question that you did  
9 ask. When the sponsor comes back in requesting 90-days  
10 wear, do we then take Mark's equation and say, well, if 7  
11 days interval between removal gives you X and you go with a  
12 relative risk higher than that, you now go to a relative  
13 risk times 6 for the next one.

14 My answer to the question that you did pose is  
15 what is the upper limit. We know what is achievable. It is  
16 not something that we a priori said we are looking for a  
17 relative risk of whatever the 7-day number is currently. We  
18 do know it is achievable.

19 The companies that come to us, the sponsors, at  
20 one level have an adversarial relationship. I mean, the  
21 regulatory agency is a barrier to entry into the  
22 marketplace. But the agency and the panel serve another  
23 function, and that is to make sure that what they do have  
24 has a degree of safety, that it doesn't come back and bite  
25 them in the butt. They really don't want to have the

1 information that we are forcing them to produce brought  
2 about by a class action lawsuit. People who were around  
3 when the first found of 60-day and 90-day lenses were  
4 developed found that the tort system was actually the one  
5 that brought about the changes. It wasn't that the FDA de  
6 facto said 7-day wear is the limit of 14-day wear is the  
7 limit. Okay? It came about because in the marketplace it  
8 was discovered that people did develop loss of vision from  
9 corneal ulcers and they demanded appropriate redress from  
10 the companies. Okay?

11 I think we can offer them that same degree of  
12 safety by setting the benchmark at what is currently  
13 achievable, and seeing if the materials and lens designs  
14 that they have meet the benchmark that is there.

15 DR. SUGAR: Currently achievable being the 20 per  
16 10,000?

17 DR. SCOTT: Whatever the number currently is.

18 DR. HILMANTEL: I think to some extent some of the  
19 panel is missing the point of the question.

20 DR. SCOTT: Do any of us have it?

21 DR. HILMANTEL: We are setting up as a benchmark  
22 that the new lenses have to be equally as safe as the old  
23 lenses, but in any statistical testing you always have some  
24 uncertainty. Even though that is what we are trying to  
25 prove, that the new lenses are equally as safe as the old

1 lenses, there is some slop in it. There is going to be some  
2 kind of confidence interval in your assessment of the risk,  
3 and we are just trying to set some kind of reasonable upper  
4 bound for the slop, for the confidence intervals. So, there  
5 is no way we can set 20 per 10,000 as the upper bound, if  
6 that is what we are trying to show. If we are trying to  
7 show that the new lenses have a risk of 20 per 10,000 there  
8 is going to be some slop in the measurement and we want to  
9 limit that, we want to limit the amount to some reasonable  
10 figure.

11 DR. BRIGHT: If I can interject here, Gene, you  
12 are already assuming that the sense is that the standard  
13 should be the same, and I wasn't sure I heard that because I  
14 heard talk about greater benefits and, therefore, we should  
15 accept greater risk. So, what is the sense now? That it  
16 should be the same or that we should accept higher risk?

17 DR. SUGAR: We have heard discussions both ways.

18 MS. NEWMAN: Yes, I agree. That is what I was  
19 going to bring up. I don't know. It depends on what the  
20 risk is.

21 DR. BRADLEY: A corneal ulcer.

22 MS. NEWMAN: No, no, the risk of that though. If  
23 you can go to 30 days with someone who can't remove them and  
24 you may have a couple more ulcers, does the benefit outweigh  
25 the risk?

1 DR. BRIGHT: Whether it outweighs the risk is a  
2 judgment call. That is not what you get out of a study.  
3 You get out of the study what the risk is. The panel  
4 already have an idea of what the benefits are. So, the  
5 question is how much risk matches that benefit in your  
6 clinical judgment.

7 DR. SUGAR: Dr. Matoba, do you want to comment?

8 DR. MATOBA: My original problem was that actually  
9 I wouldn't have even thought that the 7-day extended wear  
10 risk that you originally approved -- it would not have been  
11 acceptable to me, looking at the 20- and 30-year  
12 projections. But seeing that that has already been in  
13 practice for a number of years, I would argue with Dr.  
14 Bullimore that that should be the standard and new contact  
15 lens for 30-day wear should show equivalence to the previous  
16 7-day extended wear. For statistical purposes, I would like  
17 to suggest 2 times that as the maximum that we would accept.

18 DR. SUGAR: There is not unanimity of opinion but  
19 I think you have heard a number of opinions, and I don't  
20 know that it is worth the time to try to achieve consensus  
21 at this point. I would like to move on unless someone feels  
22 strongly we should poll the panel.

23 DR. SAVIOLA: I agree. We didn't ask you to vote  
24 on these issues. We would like to get a somewhat unified  
25 opinion but we expect that there are going to be differences

1 in people's viewpoints. So, for the purposes of continuing  
2 discussion for the remainder of the questions we have to  
3 discuss, if we could, in a sense, table the risk/benefit  
4 question and just proceed as if we are going to deal with a  
5 certain level of risk. Again, our sense is that we want to  
6 minimize any increase in what we perceive as risk, what we  
7 would measure as risk and, therefore, for the purposes of  
8 this question we get the sense that, as we pose it to you,  
9 the lower the number the better.

10 DR. SUGAR: Correct. I don't think there is any  
11 disagreement with that.

12 DR. YAROSS: I just have one technical question  
13 out of ignorance, you alluded to newer therapies. Have new  
14 available therapies reduced the likelihood of a poor outcome  
15 from an ulcer, or is that basically unchanged?

16 DR. SUGAR: I think that they were presenting that  
17 antibiotics are more available and more practitioners are  
18 using the antibiotics, that it would be harder to collect a  
19 population -- which is actually the next question -- a  
20 population of people with ulcers for a case-control study,  
21 or to in any way guarantee you are capturing all of the  
22 affected individuals because there are more and more  
23 practitioners treating them rather than sending them to  
24 referral centers. Correct?

25 DR. YAROSS: I just didn't know whether or not it

1 might contribute to risk/benefit.

2 DR. BULLIMORE: But in the context of a case-  
3 control study you don't need to guarantee that you capture  
4 all the cases.

5 DR. SUGAR: I understand that, but if you want to  
6 capture enough cases to have a case-control study and you go  
7 to X number of academic centers where they used to all be  
8 sent, you are not going to get them as readily as before.  
9 That was, I think, their point.

10 Question two, does the panel feel there would be  
11 difficulty in getting enough extended wear ulcer cases for  
12 an effective case-control study? And, Marcia's point is one  
13 of the issues in terms of being able to capture that  
14 population. Obviously, the answer to this depends on the  
15 frequency of events, which is an unknown. So, I don't know  
16 how you are going to get an opinion on this.

17 DR. HILMANTEL: Well, I just thought maybe some of  
18 the cornea people on the panel could give us some guidance  
19 as to, for example, how many contact lens ulcers they will  
20 see in a university clinic in a given year.

21 DR. SUGAR: Alice, do you want to respond?

22 DR. MATOBA: Well, I am trying to calculate how  
23 many I see, and there are four or five cornea people in our  
24 department, so I would say maybe 20 -- 15-20 per month  
25 contact lens related -- no, no, I am sorry, microbial

1 keratitis, but the majority are either trauma or contact  
2 lens related. I would say half a dozen a month.

3 DR. BULLIMORE: Mr. Chairman, would this be an  
4 appropriate time to define an ulcer?

5 DR. SUGAR: That is question number seven. It  
6 sort of deals with that.

7 DR. BULLIMORE: Okay, I will defer that question.

8 DR. SUGAR: Karen is getting agitated.

9 DR. BANDEEN-ROCHE: No, just a clarification on  
10 Dr. Matoba's answer, out of how many patients per month?  
11 You say you see about half a dozen ulcers, that is out of  
12 what total population?

13 DR. MATOBA: Well, I don't think I could estimate  
14 that off the top of my head. But we are a referral service  
15 so we see quite a few.

16 MS. NEWMAN: Is that a tertiary center then, or do  
17 you just want to get basic people out there? Do you know  
18 what I am saying to you? If that is a tertiary academic  
19 center --

20 DR. HILMANTEL: I think we can use all the  
21 information we can get. We just want a sense of how  
22 difficult a project it is going to be. So, yes, if we can  
23 get information about university centers or just private  
24 cornea specialists, private practice, any information is  
25 helpful.

1 DR. BULLIMORE: We have to be very careful. This  
2 is no disrespect to anybody on the panel, those of us who do  
3 large-scale studies of eye disease and other stuff know that  
4 when you go to a clinician and say how many cases do you see  
5 a year, you take that number and generally divide it by ten  
6 to estimate the number of cases that you might actually then  
7 be able to recruit for a study. You disagree?

8 DR. MATOBA: Not at all.

9 DR. BULLIMORE: The old joke is about the easiest  
10 way to cure disease is to study it. When you try to find  
11 these cases, they are maybe not as prevalent or as many  
12 incident cases as you want. But just a point of  
13 clarification, I mean, you personally see how many per  
14 month?

15 DR. MATOBA: Well, I mean, last week I saw three  
16 cases, but I think maybe two were contact lens related.

17 DR. BULLIMORE: Was that a typical week or a high  
18 week, low week?

19 DR. MATOBA: High-ish. So, maybe some weeks one;  
20 some weeks none; some weeks two.

21 DR. BULLIMORE: But when addressing this question,  
22 you have to think about whether you want to capture serious  
23 ulcers where you have a big sort of dripping, goopy thing on  
24 the visual axis or whether you want to consider a 1 mm  
25 epithelial break with an underlying infiltrate, you know,

1 just in from the limbus because where you go for these  
2 patients will be affected -- there will be a relationship  
3 between the setting and the severity of the cases that you  
4 see. So, where I practice and prescribe contact lenses and  
5 treating ulcers, if I saw something that was small, off the  
6 visual axis, I might feel comfortable treating that. If I  
7 saw something big, on the visual axis, I might say, okay, I  
8 could try prescribing for this but Jayne really deserves  
9 this patient and I would refer it off. So, in terms of  
10 number of cases and setting, we have to think about the  
11 severity of what we are talking about and ultimately define  
12 what is a case, or what are the things that we are looking  
13 at here.

14 DR. SUGAR: That is question seven. Mike or  
15 Jayne, do you have any other comments on prevalence of  
16 ulcers in your practices, of contact lens related ulcers in  
17 your practices?

18 DR. GRIMMETT: I can comment, but my practice up  
19 in Palm Beach County, the county responsible for fouling up  
20 the election --

21 [Laughter]

22 -- is mostly in older clientele. We don't have a  
23 lot of ulcers coming to our clinic, probably one a month  
24 perhaps. We don't have an active contact lens, younger  
25 patient population. The private practitioners generally

1 treat the patients they see with the quinolones, broad-  
2 spectrum antibiotics and generally don't refer those  
3 patients to us, at least in our northern satellite facility.

4 DR. WEISS: We have two cornea people, and I am  
5 thinking around 100 a year, but I think your point is well  
6 taken as to what we are going to call an ulcer. If it is  
7 something that is going to be visually significant or  
8 visually threatening versus a small, little infiltrate and  
9 epithelial defect peripherally. But I think those cases are  
10 out there. I mean, there are plenty of those cases out  
11 there. So.

12 DR. SUGAR: Jose, who doesn't see ulcers?

13 DR. PULIDO: I thought you all had accepted before  
14 that benchmark of -- what was it? -- but what I remember  
15 from the article, there was a definition of what they used  
16 as ulcer. So, if you are going to now change the definition  
17 of what an ulcer is, can you use the same benchmark as you  
18 had before?

19 DR. SUGAR: Anything that the practitioner felt  
20 was an ulcer. There were the same people doing both  
21 studies, and in the second study they made phone calls and  
22 asked people to list how many they had seen and they sort of  
23 left it to the practitioner to define.

24 DR. BULLIMORE: If we are going to use the same  
25 criterion as the other studies, fine, but as long as they

1 are well defined. You know, I hear comments on the right,  
2 here, of course, I know what an ulcer is. I know what it is  
3 when I walk into my consulting room but, of course,  
4 everybody will have their own definition and everybody will  
5 draw their own line in the sand as to what they call an  
6 ulcer and what they call microbial keratitis and what people  
7 call all the other fancy names that we come up with for a  
8 contact lens related complication. You know, does it have  
9 to be culture positive? Does it have to leave a scar? Does  
10 it have to leave any damage to visual acuity? But in terms  
11 of, you know, assessing the actual risk to the population,  
12 those are all important questions.

13 DR. SUGAR: In the Poggio study it was defined as  
14 a corneal stromal infiltrate with an overlying epithelial  
15 abnormality, parentheses, ulceration, end parentheses --  
16 clinically diagnosed as microbial keratitis, received  
17 antibiotic treatment for presume microbial keratitis.

18 DR. BULLIMORE: If that is what we are going to  
19 keep as our definition, fine, but let's have it explicit  
20 rather than, "oh, I know what an ulcer is."

21 DR. SUGAR: Enough said?

22 Number three, what statistical power would the  
23 panel recommend to ensure confidence in the result? Pick a  
24 number, 0.8, 0.95? Karen?

25 DR. BANDEEN-ROCHE: My only comment would be that