

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

**Joint Meeting of the
OPHTHALMIC DRUGS SUBCOMMITTEE OF THE
DERMATOLOGIC AND OPHTHALMIC DRUGS
ADVISORY COMMITTEE
and the
ENDOCRINE AND METABOLIC DRUGS ADVISORY COMMITTEE**

**Wednesday,
March 11, 1998**

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Gaithersburg Holiday Inn
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1 P R O C E E D I N G S (8:35 a.m.)

2 DR. BONE: Good morning. If the participants
3 will please take their seats. We may have one or two
4 people who will be joining us shortly, but I think all
5 things considered, it's show time.

6 I'm Dr. Henry Bone. I'm the chair of the
7 Endocrine and Metabolic Drugs Advisory Committee. We are
8 sitting here today with the Ophthalmology Advisory
9 Subcommittee, and we're going to be discussing diabetic
10 retinopathy clinical trial endpoints. We will first, I
11 think, go around introducing the people who are at the
12 front table, followed by the conflict of interest statement
13 from Ms. Riley, and then we'll go onto the next step.

14 DR. WEINTRAUB: I'm Michael Weintraub, director
15 of the Office of Drug Evaluation No. 5.

16 DR. CHAMBERS: I'm Wiley Chambers. I'm the
17 deputy director for the Division of Anti-Inflammatory
18 Analgesics and Ophthalmologic Drug Products.

19 DR. FEMAN: I'm Steve Feman. I'm an
20 ophthalmologist and professor of ophthalmology at
21 Vanderbilt University.

22 DR. MOLITCH: I'm Mark Molitch, an
23 endocrinologist at Northwestern University in Chicago.

24 DR. SPELLMAN: I'm Frank Spellman, a retinal
25 specialist private practitioner here in the Washington,

1 D.C., area and served for 14 years as head of the retina
2 service at Howard University Hospital.

3 DR. ZAWADZKI: Good morning. I'm Joanna
4 Zawadzki. I'm an endocrinologist in private practice in
5 this area, and I'm clinical associate professor at
6 Georgetown University.

7 DR. SLOAN WILSON: I'm Sloan Wilson from Little
8 Rock, Arkansas, and Rye, New Hampshire, and I'm semi-
9 retired. I'm professor emeritus of ophthalmology at the
10 University of Arkansas and also still in private practice
11 doing retinal work.

12 MS. RILEY: I'm Tracy Riley. I'm the executive
13 secretary to the Dermatologic and Ophthalmic Drugs Advisory
14 Committee.

15 DR. BONE: Henry Bone, endocrinologist,
16 Detroit, Michigan, and chair of the E&M Drug Advisory
17 Committee.

18 DR. SEDDON: Johanna Seddon, ophthalmologist,
19 retina specialist, and epidemiologist, associate professor
20 of ophthalmology at Harvard Medical School and
21 Massachusetts Eye and Ear Infirmary in Boston.

22 DR. MINDEL: Joel Mindel from the Departments
23 of Ophthalmology and Pharmacology, Mount Sinai Medical
24 School in New York City.

25 DR. DAVIDSON: Jaime Davidson, Endocrine and

1 Diabetes Associates, and an associate professor at
2 Southwestern Medical School.

3 DR. CARNEY: I'm Marcia Carney, associate
4 professor of ophthalmology, Medical College of Virginia,
5 retina specialist.

6 DR. FREEMAN: Bill Freeman, professor of
7 ophthalmology at UC-San Diego and a retinal surgeon.

8 DR. BONE: Thank you.

9 I'd like to also acknowledge the important role
10 of Kathleen Reedy, executive secretary of the Endocrine and
11 Metabolic Drugs Advisory Committee, in helping prepare for
12 the meeting.

13 I want to remind everyone to speak clearly and
14 identify themselves, speak into the microphone. That
15 applies to the members of the committee and others who may
16 make remarks during the session today.

17 Ms. Riley?

18 MS. RILEY: Thank you.

19 The following announcement addresses the issue
20 of conflict of interest with regard to this meeting and is
21 made a part of the record to preclude even the appearance
22 of such at this meeting:

23 Since the issues to be discussed by the
24 committee will not have a unique impact on any particular
25 firm or product, but rather may have widespread

1 implications with respect to entire classes of products, in
2 accordance with 18 USC 208, waivers have been granted to
3 each member and consultant participating in the committee
4 meeting. A copy of these waiver statements may be obtained
5 from the agency's Freedom of Information Office, Room 12A-
6 30, Parklawn Building.

7 In the event that the discussions involve any
8 other products or firms not already on the agenda, for
9 which an FDA participant has a financial interest, the
10 participants are aware of the need to exclude themselves
11 from such involvement, and their exclusion will be noted
12 for the record. With respect to all other participants, we
13 ask in the interest of fairness that they address any
14 current or previous financial involvement with any firms
15 whose products they may wish to comment upon.

16 DR. BONE: Thank you very much, Ms. Riley.

17 On the agenda, we have a spot here for Open
18 Public Hearing 1. There's another spot after the
19 presentations, at the beginning of the afternoon. No one
20 has registered with Ms. Riley to participate in the morning
21 segment. I don't see anyone asking to. Anyone who decides
22 that they wish to make remarks during the afternoon open
23 public hearing, please sign up with Ms. Riley with your
24 name and affiliations before the end of the lunch break.
25 Thank you.

1 We're now 4 minutes ahead of schedule, thanks
2 to the cooperation of all those people who did not make
3 remarks during Open Public Hearing 1, and we welcome Dr.
4 Wilson.

5 The next item here is the introductory remarks
6 from Dr. Chambers.

7 DR. CHAMBERS: Thank you.

8 I would just like to welcome everyone. I
9 understand that this may be a relatively new forum for many
10 of you. The Ophthalmic Subcommittee is part of the
11 Dermatologic and Ophthalmic Advisory Committee, and as
12 such, we will typically meet as a subcommittee and may
13 invite additional representatives from a particular field
14 that we're discussing. In this case, we're looking at
15 diabetic retinopathy and have added additional retinal
16 specialists, as well as people from the Endocrine Advisory
17 Committee.

18 So understanding that this may be new for
19 people, please feel free to ask questions. I remind
20 everybody to try and speak into the microphone.

21 The purpose for this is to try and provide
22 guidance to the agency so that the agency can better help
23 sponsors of applications for products for diabetic
24 retinopathy in various forms and its various
25 manifestations. Currently, we do not have any products

1 that are specifically approved for the treatment of
2 diabetic retinopathy, with the possible exception of some
3 of the insulin products and their indirect effects on
4 diabetic retinopathy, but no products specifically targeted
5 just for diabetic retinopathy.

6 Because of the expectation that many of these
7 trials will take a long period of time, we would like to
8 try and be able to provide guidance for companies early on
9 and not just have studies come in several years down the
10 road and say, "Well, we didn't study the right endpoints,
11 we don't think this is appropriate, go back and do new
12 trials that are 3 or 4 or 5 years long." We'd like to try
13 and provide as much as possible up front. We recognize the
14 science may change, we may learn different things as we go
15 along, but we'd like to try and capture the best that we
16 can as of March of 1998.

17 Thank you.

18 DR. BONE: Thank you very much, Dr. Chambers.

19 Obviously, the specific emphasis here has been
20 on the development of products which are particularly
21 directed toward the treatment or prevention of diabetic
22 retinopathy, but the discussion will have implications for
23 the evaluation of diabetic retinopathy in studies of drugs
24 for the control of diabetes as well, I'm quite sure. So
25 this is, I think, of very broad interest ultimately.

1 Now, I believe there will be a series of
2 presentations in the next segment. The program lists Drs.
3 Aiello, Davis, and Ferris. Is that the order of the
4 presentation?

5 DR. AIELLO: Not quite.

6 DR. BONE: Oh. Well, who's next?

7 DR. AIELLO: Aiello, Ferris, and then Davis.

8 DR. BONE: Fine. Thank you. If the next three
9 speakers will, then, each introduce themselves and make
10 their remarks, we'd appreciate it very much.

11 Dr. Aiello?

12 DR. AIELLO: Thank you very much, Dr. Bone, and
13 other members here today. It is a pleasure for us to have
14 this opportunity to present to the joint committee here
15 today. I am Lloyd Paul Aiello, assistant professor of
16 ophthalmology at the Joslin Diabetes Center at Harvard
17 Medical School. By way of disclosure, I am a non-paid
18 consultant for Eli Lilly and Company, although they do
19 reimburse my travel expenses in that regard, but that is
20 the extent of the involvement.

21 Later on today you will also hear from Dr.
22 Frederick Ferris, who's director of the Division of
23 Biometry and Epidemiology at the National Eye Institute,
24 National Institutes of Health, and following his
25 presentation you'll hear from Dr. Matthew Davis, who's

1 director and professor emeritus of the Fundus Photograph
2 Reading Center at the University of Wisconsin, and then
3 there will be a very short summary by myself to follow
4 after that.

5 Now, for the purposes of the rest of the
6 presentation today, what we'd like to do is focus very
7 directly on the more severe complication endpoints of
8 diabetic retinopathy, and in particular proliferative
9 diabetic retinopathy and the prevention of sight-
10 threatening macular edema. As most of you are aware, one
11 of the reasons for focusing on this area is due to the fact
12 that we're in a very exciting scientific and therapeutic
13 crossroad in the development of new therapies for the
14 treatment of the complications of diabetic retinopathy.
15 This arises primarily through the accomplishments over the
16 past two decades, which fundamentally have involved a much
17 improved understanding of the biochemical mechanisms
18 underlying the development of these complications.

19 As a result, there's been a development of a
20 series of drugs which may alter these mechanisms and, thus,
21 could have therapeutic potential. The consequences of
22 these accomplishments, therefore, is that we now have
23 potential therapies for sight-threatening complications of
24 diabetic retinopathy, and, indeed, numerous agents of these
25 are beginning or approaching clinical trial.

1 Now, these new therapeutic approaches which are
2 aimed at preventing some of these stages of retinopathy
3 actually have the capability of potentially preventing the
4 development of the current stages of retinopathy, which we
5 use as the indication for initiating therapeutic
6 intervention. Thus, the investigation of these new
7 approaches will necessitate a reevaluation of the
8 traditional outcome measures for determining clinical
9 efficacy in clinical trials.

10 So for this presentation, the general aim will
11 be to recommend outcome variables with clinical benefit
12 which are suitable for trials evaluating the efficacy of
13 new pharmacological agents which are intended to slow or
14 prevent the development of proliferative diabetic
15 retinopathy or sight-threatening diabetic macular edema.
16 More specifically, we would like to define reproducible and
17 clinically beneficial outcome variables for patients with
18 diabetic macular edema and severe non-proliferative
19 diabetic retinopathy, and we'd like to do this in a way
20 that they will be useful endpoints for demonstrating
21 efficacy in masked, randomized, placebo-controlled trials.

22 Now, most of us will agree that visual function
23 is the most important outcome variable. However, for these
24 studies, visual acuity itself is a difficult primary
25 outcome variable for a variety of reasons, not only due to

1 the slow rate of progression of visual loss in diabetic
2 retinopathy, but also because vision may remain unaffected
3 for many years, despite very significant progression of the
4 retinopathy or actual presence of very severe retinopathy
5 itself. In addition, the effectiveness of laser
6 photocoagulation in preserving vision further compounds
7 this issue.

8 Now, as we all know, diabetic retinopathy
9 progresses through a series of stages that are relatively
10 well defined, and, indeed, for the purpose of clinical
11 trials, these have been rigorously defined.

12 After this, we'll look into things for
13 seasickness that might work as well.

14 (Laughter.)

15 DR. AIELLO: Anyway, in terms of diabetic
16 retinopathy, I was saying it progresses through a series of
17 defined stages, and for the purpose of clinical trials,
18 these are often used by comparison to standardized
19 stereoscopic fundus photographs read at a centralized
20 reading center. One of the ways this has been done is
21 through the development of severity scales, such as the
22 ETDRS retinopathy severity person scale, which is a
23 rigorously defined scale that's been well established and
24 considers both eyes of a patient in setting the level.

25 Now, by way of history, it may be important to

1 look back at what other major trials have been done in
2 diabetic retinopathy and what the outcome variables have
3 been. One of the earliest large studies is a diabetic
4 retinopathy study of 1976. In this study, it was evaluated
5 whether or not panretinal photocoagulation was effective in
6 preventing severe visual loss from proliferative diabetic
7 retinopathy. Here the outcome variable was a visual
8 variable, severe visual loss, which is defined as 5/200 or
9 worse on two consecutive visits at least 4 months apart.
10 In this study, treatment did reduce the incidence of severe
11 visual loss by 50 percent.

12 The next major trial is the ETDRS trial, the
13 early treatment diabetic retinopathy study of 1985, at
14 least part of which looked at the ability of focal laser
15 photocoagulation to prevent visual loss from macular edema.
16 Here again, the outcome variable was vision, defined as
17 moderate visual loss or a doubling of the visual angle, or
18 sometimes referred to as a three-line loss on the ETDRS
19 vision chart. Here again, the treatment reduced the
20 incidence by 50 percent, although the therapy was not
21 effective at improving visual acuity.

22 Now, as we move to some of the more recent
23 studies, we see that we've run into problems using vision
24 as a primary outcome variable and have moved into using
25 progression of retinopathy. The Sorbinil retinopathy trial

1 of 1990 looked at the ability of this drug to slow the
2 progression of early stages of diabetic non-proliferative
3 retinopathy, and here they looked at the ETDRS person
4 scale, but the treatment was not shown to be effective.

5 More recently, the large diabetes control and
6 complications trial of 1993 was performed, which looked at
7 the ability of intensive insulin therapy to either slow the
8 onset of any diabetic retinopathy or the progression of
9 mild non-proliferative retinopathy. Here the outcome
10 variable was, again, progression of three more steps along
11 the ETDRS person scale, and in this study this progression
12 was reduced by significant margins.

13 So what are the difficulties that we have with
14 the current outcomes, particularly if we're looking at
15 pharmacologic agents whose direction of action is thought
16 to be at preventing the development of proliferative
17 disease or sight-threatening macular edema? Well, the
18 ETDRS person scale is based on looking at the level of
19 retinopathy in both eyes. However, in some instances, it
20 is desirable to evaluate a single eye. This would clearly
21 be the case when the fellow eye is ineligible for treatment
22 -- perhaps it had severe disease and already had laser
23 treatment, perhaps the other eye didn't exist or the view
24 to the back of the eye to evaluate the retina was
25 inadequate -- but in the study eye, it had a level of

1 retinopathy that should be treated. Indeed, there are
2 likely to be many patients in the general population that
3 fit into this scenario, and, therefore, allowing the
4 evaluation of a single eye could more closely represent the
5 real-life situation.

6 So under the specific proposals you'll hear
7 from us in a couple of minutes is to demonstrate that a two
8 or more step change on the ETDRS eye scale is equivalent to
9 the currently accepted three or more step change on the
10 ETDRS person scale and, thus, could be used as a parameter
11 where only one eye is being evaluated.

12 Now, further difficulty comes in when one
13 starts to address other aspects, particularly macular
14 edema, because the ETDRS severity scale is based primarily
15 on the level of non-proliferative diabetic retinopathy and
16 some on the level of proliferative diabetic retinopathy,
17 but it is entirely unsuitable for evaluating diabetic
18 macular edema. Therefore, one of the other specific
19 proposals you'll hear is that we wish to establish stages
20 of diabetic macular edema which are of clear clinical
21 significance.

22 So what are the specific primary outcome
23 variables that we suggest? Well, for the evaluation of
24 macular edema, we feel that a clinically beneficial
25 endpoint is the ability to slow or prevent retinal

1 thickening or hard exudate with adjacent retinal thickening
2 which involves the center of the macula. In addition to
3 this, since there are times when the macular edema may be
4 progressing dramatically or may be approaching the center
5 and clinicians, rightly so, maybe feel compelled to treat,
6 we also feel that another beneficial endpoint would be to
7 prevent photocoagulation for macular edema in which the
8 center of the macula is documented to be imminently
9 threatened, and you'll hear more about these definitions in
10 a few moments.

11 Now, with regard to proliferative diabetic
12 retinopathy, the proposed outcome variables are really just
13 a modification of ones that we already have. We feel that
14 it is a clinically beneficial endpoint to slow or prevent
15 documented proliferative diabetic retinopathy if there's
16 been at least a three or more step change on the ETDRS
17 person scale when both eyes in a patient are to be
18 evaluated, or when there's been a two or more step change
19 on the eye scale when only a single eye in a patient is to
20 be evaluated.

21 Immediately to follow my initial presentation
22 here, you'll hear from Dr. Ferris, who will discuss the
23 clinical benefits of these various endpoints.
24 Specifically, he will address retinal thickening at the
25 center of the macula and its association with visual loss,

1 the compromise of anatomically critical structures this
2 entails, and its association with laser photocoagulation.
3 In addition, Dr. Ferris will discuss proliferative diabetic
4 retinopathy and its association with severe visual loss and
5 blindness and its association with photocoagulation.

6 Following Dr. Ferris' presentation, Dr. Davis
7 will present the justification for the specific endpoints.
8 Specifically, he'll demonstrate that a two or more step
9 change on the ETDRS eye scale is equivalent to a three or
10 more step change on the ETDRS person scale and, thus,
11 hopefully establish that a two or more step change on the
12 ETDRS eye scale is a suitable clinically beneficial outcome
13 variable for trials evaluating the development of
14 proliferative diabetic retinopathy when studying a single
15 eye. In addition, with regard to macular edema, he will
16 discuss, again, the involvement of retinal thickening or
17 hard exudate with adjacent retinal thickening involving the
18 center of the macula and photocoagulation for macular
19 edema, in which the center of the macula is documented to
20 be imminently threatened.

21 At this point, then, I'll turn the podium over
22 to Dr. Ferris.

23 DR. FERRIS: Thank you, Lloyd, Dr. Bone, and
24 everyone assembled. I'd like to start out by saying that
25 there may be some confusion about my representation here or

1 my affiliation with Eli Lilly. I'm not affiliated with Eli
2 Lilly. I don't get any support by them. The National Eye
3 Institute, however, does and has developed a memorandum of
4 understanding with Eli Lilly to help bring one of their new
5 potential treatments for diabetic retinopathy to fruition,
6 hopefully. So to that extent, the National Eye Institute
7 is working with Eli Lilly.

8 My view of this is that my job as the head of
9 the Clinical Trials Branch of the National Eye Institute is
10 to help bring new treatments to fruition, and that can be
11 with industry or it can be as I've spent 20 years or more,
12 I guess, of my life doing, without industry, as a
13 representative of the National Eye Institute. So with that
14 little -- I don't know whether that's a disclaimer or a
15 claimer, I'll press on.

16 What I'd like to do is talk about outcome
17 variables as I see it, as someone who has been doing
18 research in this area for the last 25 years. As Lloyd
19 pointed out, in the diabetic retinopathy study, severe
20 vision loss was used as an outcome variable. The early
21 treatment diabetic retinopathy study also used severe
22 vision loss, but also developed an outcome variable that we
23 called moderate vision loss, which was a three-line change,
24 a doubling of the visual angle, on a logarithmic visual
25 acuity chart. The Sorbinil retinopathy trial, which was

1 one of the National Eye Institute's previous forays into a
2 collaboration with the drug company Pfizer, in this case,
3 to look at an aldose reductase inhibitor, used a two-step
4 worsening of retinopathy. That was modified -- I was
5 involved on the data monitoring committee of the diabetes
6 control and complications trial. In that study, we thought
7 a three-step worsening of retinopathy was a more
8 reproducible and less variable outcome variable, so that
9 was the outcome variable that was used in that study.

10 You might note that none of these studies has
11 ever come to the FDA for an NDA, because they've either
12 been photocoagulation treatments or tightening of control
13 didn't require a new drug. The only one that was a new
14 drug was the Sorbinil retinopathy trial, and that didn't
15 come because it didn't work.

16 Well, over the last several years, I think
17 almost a dozen different companies have come to me, as the
18 chief of the Clinical Trials Branch at NEI, to discuss
19 possible new therapies for diabetic retinopathy, and some
20 of these, I think, are quite promising, but it has pointed
21 out that we currently have a problem with regard to outcome
22 variables for proliferative retinopathy and diabetic
23 macular edema in particular. I say these in particular
24 because I think there are a number of potential new
25 treatments in both of these areas, and unless we develop

1 outcome variables, we're not going to be able to add new
2 treatments.

3 Now, proliferative retinopathy itself, as far
4 as I'm concerned, is a bad outcome for the patient. It's
5 not a surrogate outcome, it's a bad outcome, and it's a bad
6 outcome because it's associated with blindness and because
7 it usually is an indication for photocoagulation, and I
8 think from many patients' point of view, photocoagulation
9 is a bad outcome. Lest anybody think it's not a bad
10 outcome, I'll be happy to take them down to Bethesda, and
11 we can put in some laser burns and see how you -- nobody
12 would like this. This is a bad outcome for the patient,
13 not just from the point of view of the cost, but also from
14 the point of view that it is an ablative and destructive
15 procedure by nature. So avoiding photocoagulation would be
16 a potential benefit for a patient.

17 Well, what about severe vision loss? What I
18 did was, for this meeting, I went back to the ETDRS data
19 set, and I said, "What is your risk, even given current
20 treatment, for developing severe vision loss?" Now, as you
21 can see on this slide, even with photocoagulation -- these
22 happen to be eyes that were assigned to deferral of scatter
23 photocoagulation. The eyes assigned to early treatment
24 would have a similar rate. It would be slightly less. It
25 would be down to about 3.5 percent at 5 years. But what

1 this points out is that if you develop proliferative
2 retinopathy, your risk of severe vision loss, which is
3 defined as visual acuity of 5/200 or worse at two
4 consecutive visits, is 12 times higher than if you didn't
5 develop proliferative retinopathy, and I suspect that some
6 of these no proliferative retinopathies were because we
7 never documented them because they had a vitreous
8 hemorrhage and we never could actually prove that they had
9 proliferative retinopathy. So the risk is probably higher
10 than 12. The relative risk.

11 Now, the recommendations that I would like to
12 see and I think that all of us who are presenting would
13 like to see is to take this three-step retinopathy change
14 and use it as an outcome for studies of new treatment that
15 might prevent the development of proliferative retinopathy,
16 which, as I said, I think would be something that might be
17 valuable for patients. As Lloyd mentioned, there are
18 reasons that we may want to look at a single eye and not a
19 patient, and most of those reasons have to do with the
20 other eye either not being available or already having
21 photocoagulation or being blind, and we think that single
22 eye studies should be allowed, as long as the eye is
23 identified at the beginning of the trial and, at least in
24 my view, randomly assigned to different treatments.

25 Photocoagulation itself is a reasonable bad

1 outcome for a patient, but as I'll discuss, it has some
2 problems as an outcome variable because it may be variably
3 applied, and what we would like to propose is a method of
4 documentation of progression at the time of
5 photocoagulation.

6 Finally, an outcome variable that I think would
7 be reasonable to discuss, given the number of new anti-
8 angiogenic treatments, is progression of neovascularization
9 or regression of neovascularization that already exists,
10 and there are a number, as you know, of new anti-angiogenic
11 approaches that are near the stage of getting to human
12 study.

13 Well, diabetic macular edema is the other area
14 where I think we need to modify our outcome variables. I
15 would say that for proliferative retinopathy, what we're
16 proposing is really just tightening up what already existed
17 with regard to the three-line or two-step change in
18 retinopathy. For diabetic macular edema, we need a new
19 outcome variable. As you know, diabetic macular edema is
20 associated with vision loss, and if there were no other
21 treatments, I think the three-line change in visual acuity
22 that we used previously would be a good outcome variable.
23 However, the standard of care now is initiating
24 photocoagulation often before any visual acuity loss has
25 occurred, and it is quite effective at preventing visual

1 acuity loss, so it makes visual acuity itself a difficult
2 variable for us as an outcome variable.

3 Just as a quick review, in the ETDRS we define
4 diabetic macular edema as any retinal thickening in the
5 macular area. For purposes of managing patients, we
6 subdivided this into a group that we call clinically
7 significant macular edema, and that categorization had
8 three subgroups, and as I'll show you, I think one of the
9 subgroups is more vision threatening than the other two,
10 and that is retinal thickening that already involves the
11 center of the macula or the fovea. That, I think, is by
12 far the most serious of these.

13 These other two we thought of as indications
14 that the macula was threatened. That is, if there was hard
15 exudate or retinal thickening within 500 microns of the
16 center of the macula or retinal thickening -- and this
17 little doodad here is what my PowerPoint program, I guess,
18 thought was a greater-than-or-equal-to sign, so it's
19 greater than or equal to one disc area within this diameter
20 of the center of the macula. So the idea here being a
21 fairly large area of edema that is within 1,500 microns of
22 the center, we were using in the ETDRS as an indication for
23 photocoagulation.

24 Well, what about these with regard to their
25 risk of vision loss? Now, here I've taken the eyes

1 assigned to deferral. That's not to imply that these eyes
2 never got photocoagulation, because as you know, after
3 about an average of 2 and a half years into that study,
4 photocoagulation was shown to be effective, so that most of
5 these eyes eventually got photocoagulation. But ignoring
6 the fact that there's a combination of no treatment and
7 treatment here, you can see that the risk of a three-line
8 loss is considerably higher if you had thickening at base
9 line than if you had the other two aspects of clinically
10 significant macular edema or greater yet than if you had
11 macular edema that was not yet clinically significant.

12 I might also point out that that group, macular
13 edema not yet clinically significant, virtually has to go
14 through the clinically significant phase to lose vision,
15 and also the center essentially has to be involved if
16 vision is going to be down from the macular edema.

17 What if we look at this a slightly different
18 way, and that is, this is the same line, center definitely
19 involved at base line and, again, about a 36 percent or
20 more risk of a three-line visual acuity loss, and as I
21 think is not surprising, if the center ever became involved
22 during follow-up, you have a similar result. This was
23 people that didn't have the center involved at the start,
24 but it eventually became involved, and, again, a relatively
25 low rate if the center was never involved. Many of those,

1 I suspect, are from vitreous hemorrhage, and we have that
2 problem in diabetic retinopathy. They're competing risks
3 for vision loss.

4 Now, what we think is a reasonable outcome
5 variable is, if you are studying eyes at risk of
6 progression, either already having macular edema or perhaps
7 just having diabetic retinopathy, we think a reasonable
8 outcome variable is retinal thickening that involves the
9 center. Because you may need to treat for the standard of
10 care even prior to the center being involved, we would like
11 to define something defining the center as imminently
12 threatened as a way of documenting the need for
13 photocoagulation, because as I mentioned, I think
14 photocoagulation alone, although it sounds like a great
15 outcome variable, is a little problematic.

16 Well, why not just use visual acuity? As I
17 mentioned, I think visual acuity is a great outcome
18 variable and should be used in any study, but it may not be
19 possible to use it as the primary outcome variable. I
20 think there's general agreement in the community that a
21 three-line change in visual acuity is a clinically
22 important change. A two-line change, I think, is probably
23 for the most part also important, and there's more than a
24 95 percent chance, at least done the way we do it, that a
25 two-line change is not due to random fluctuation, but is in

1 fact either a worsening or an improvement, depending on
2 which direction the two-line change is.

3 The problem here is the visual acuity is
4 affected -- and markedly affected -- by photocoagulation,
5 and the photocoagulation, depending on how it's applied,
6 may induce a confounding and bias in the outcome
7 assessment. If we don't use visual acuity as a primary
8 outcome variable, I do think we need to use it as a
9 secondary outcome variable. Visual acuity is clearly the
10 best measurement that we have of the summation of how is
11 the eye doing, so we believe that it has to be an outcome
12 variable, but as I mentioned, we think there's a problem
13 with using it as the primary outcome variable.

14 As I mentioned, I think photocoagulation is an
15 important outcome, but that it can be influenced by a
16 number of factors, such as how the patient's doing, what
17 the change has been, what's going on with the patient's
18 other eye, so that there are clinical- and patient-related
19 factors with regard to initiation of photocoagulation, and
20 this at least adds to a potential for bias and confounding.
21 What I'd like for you to consider is, suppose even in a
22 masked trial that there are ways of unmasking it. This
23 would not actually be very unusual. Color of the pills may
24 be slightly different, the patients may have slight side
25 effects of the medication that tends to unmask them as to

1 whether they're on active treatment or not on active
2 treatment, and I would suggest that people who are not on
3 active treatment may be more likely to receive
4 photocoagulation.

5 If the clinician is seeing a patient who he or
6 she thinks is worsening somewhat and thinks that they are
7 not on active treatment, they may be more likely to
8 intervene with photocoagulation than if he or she thinks
9 that this is a patient on active treatment and maybe we
10 should just give this treatment a little more chance to
11 work. Well, that kind of tendency can, in my view, destroy
12 a study, and I don't know any way to guarantee that that
13 isn't happening. So that's why, in my view, we should
14 document progression to count it as an event, that we can't
15 just use photocoagulation alone.

16 So we think photocoagulation is a definite
17 patient outcome. We think it should be included as an
18 event. It should probably be included as a secondary
19 outcome variable, but I think that we should try to
20 document worsening of retinopathy in order to count it as a
21 definite event.

22 Now, with regard to demonstrating what we think
23 that documentation might be, Dr. Matthew Davis from the
24 Fundus Photograph Reading Center at the University of
25 Wisconsin will help describe the methods that we think we

1 can use to document progression.

2 DR. DAVIS: Good morning. It's a pleasure to
3 be here. My principal professional interest for the last
4 30 years has been diabetic retinopathy, its natural course,
5 treatment, and methods of assessment. My colleagues at the
6 University of Wisconsin-Madison Fundus Photograph Reading
7 Center and I have participated in many clinical trials in
8 this area, both NIH-supported and pharmaceutical company-
9 supported. We are eager to participate in the design and
10 conduct and analysis of such trials, particularly of agents
11 that may slow the progression of retinopathy to vision-
12 threatening stages.

13 I am currently collaborating as a paid
14 consultant at Eli Lilly and Company in the design of such
15 trials, and it is likely that we will serve as the Fundus
16 Photograph Reading Center for them. My interest in
17 outcomes for diabetic retinopathy studies, though, is not
18 limited to the Eli Lilly Company.

19 Non-simultaneous stereoscopic color fundus
20 photography provides a convenient non-invasive method for
21 observing and documenting the clinical characteristics of
22 diabetic retinopathy. In conjunction with the Early House
23 symposium on diabetic retinopathy, supported by the U.S.
24 Public Health Service in 1968, a classification of diabetic
25 retinopathy using such photographs was developed and

1 subsequently modified. This classification uses a
2 combination of standard photographs and written definitions
3 to define from three to six severity steps or grades for
4 each of the normalities comprising the clinical picture of
5 diabetic retinopathy. Most abnormalities are graded in
6 five or six of the seven somewhat overlapping 30-degree
7 circular areas, which we call the standard photographic
8 fields that are photographed in each eye.

9 The slide you're looking at shows these seven
10 fields for a right eye. One field is centered on the optic
11 disc -- the little circle here is the optic disc -- and
12 another field is centered on the macula, another one is a
13 little bit temporal to the macula, and then there are four
14 more in each of the four quadrants. On this diagram, this
15 line is the equator of the globe, so you can see that
16 there's a lot of retina that we're not photographing, but
17 most of the action in diabetic retinopathy is back here.

18 Now, in this grading system, we use photographs
19 or written definitions to define several grades, and here
20 I'm giving you two examples: first of all, new vessels on
21 the disc, and this, as you can imagine, is graded only in
22 Field 1, the field that has the disc in it. You can't
23 grade new vessels on the disc if you don't have a picture
24 of the disc. So absent, questionable, which in our usage
25 is probable -- if the grader thinks that there's a 50 to 90

1 percent chance that they're right in saying that this
2 lesion exists, they call it questionable, and if they're
3 very sure that the lesion exists, they call it definite.

4 In this case, the cut point between Grade 2 and
5 Grade 3 is the standard photograph that has about a quarter
6 to a third of a disc area of new vessels in it, and then
7 the next cut point between Grade 3 and Grade 4 is another
8 standard photograph, 10c, that has about a disc-and-a-half
9 area of vessels in it.

10 The scale for new vessels elsewhere is slightly
11 different. The first cut point between definite and
12 moderate is not a photograph, but is a written definition,
13 new vessels that cover about a half-disc area of retina.
14 And then the next cut point between moderate and severe is,
15 again, a standard photograph.

16 The grade for that lesion in that one field is
17 the grade for the eye, but it's more complex for lesions
18 that are graded in several fields, and that complexity is
19 reduced -- in order to get a grade for an eye is reduced by
20 first looking for the photographic field that has the most
21 severe grade, in this case, for new vessels elsewhere and
22 then asking -- for instance, let's say the most severe
23 grade is new vessels but less than a half-disc area. Then
24 the question is, do we see that in only one field, or do we
25 see it in two or three fields, or do we see it in four or

1 five fields? So we now get a longer scale. We get a scale
2 with three, six, nine, twelve steps in it for these lesions
3 that are graded in several fields.

4 Now, the next step in this process is to put
5 together the grades for various lesions, such as
6 hemorrhages and microaneurysms, cotton wool spots,
7 intraretinal microvascular abnormalities, which is IRMA,
8 and then to produce a series of severity levels that
9 reflect the risk of progression to severe visual loss or to
10 a more severe level. So here's Level 10, no retinopathy.
11 That's easy, diabetic retinopathy is absent. The next
12 severity level on this scale is Level 20, and there's
13 nothing between 10 and 20. We just use two digits here
14 because in an earlier version of the scale, we used 1, 2,
15 3, 4, 5, and we want to be able to relate back to that
16 earlier version. So there aren't any steps in between
17 these numbers. Twenty is very mild non-proliferative
18 retinopathy -- that is, microaneurysms only -- and so
19 forth.

20 You've probably finished reading this slide. I
21 don't need to read it to you, but I'll just point out four
22 important levels in regard to our presentation today. One
23 is 47, which is the more severe of two grades that we call
24 moderate; another is 53, that we characterize as severe
25 NPDR; 61 is very mild proliferative retinopathy -- that is,

1 new vessels away from the disc only and less than a half-
2 disc area, so that's mild PDR; then the next level, 65,
3 which we characterize as moderate, in that category go eyes
4 that have more new vessels elsewhere than a half-disc area
5 or eyes that have any new vessels on the disc at all; and
6 then the next level up is high-risk, and that's familiar
7 to, I think, all ophthalmologists.

8 Now, it gets even more complex when we consider
9 both eyes of a patient. We've just talked about the scale
10 for an eye, but we all come with two eyes, so now we have a
11 more complicated scale. The first step on this more
12 complicated scale is 10 in the more severe eye and 10 in
13 the less severe eye, meaning no retinopathy in either eye.
14 So the next step on the scale, Step 2, is Level 20, which
15 you remember was microaneurysms only in one eye and
16 something less than that in the other. Well, the only less
17 than that is 10, so here is a patient who has
18 microaneurysms only and in only one eye.

19 The next step on the scale is the patient with
20 microaneurysms only in both eyes, and so on, up we go,
21 until we get to the patient who has high-risk proliferative
22 retinopathy in one eye, and then high-risk in both eyes.
23 All of these 70s are increasing degrees of high risk, and
24 the 80s are eyes that we can't really classify because they
25 have a lot of hemorrhage in them.

1 Now, what about the reproducibility of these
2 scales? Using eyes from the ETDRS, if we use the eye scale
3 -- and you just saw, there are more than six steps in the
4 eye scale, but in this data set, only six steps were
5 exercised -- we find there are two important things on this
6 slide. One is complete agreement between graders. This is
7 reproducibility graded once by one grader and then later on
8 by another grader. Complete agreement is not as good as
9 we'd like. It's about 50 percent, sometimes not even 50
10 percent. Agreement within one step is a lot better, and if
11 you imagine the grader comparing an unknown eye with the
12 standard eyes, there are going to be a lot of eyes that are
13 very close to the standard, and on one day the grader may
14 say, "Well, that's equal to the standard or a little more,"
15 and then another day the grader may say, "That's a little
16 less than the standard."

17 So there's a big edge effect in a categorical
18 grading system like this. This is not like measuring blood
19 glucose or creatinine. We don't get reproducibility that
20 good, but it gets pretty good within one step on this eye
21 scale, and on the longer patient scale, it isn't even quite
22 that good within one step. But it's good within two steps.
23 This is one of the reasons that the DCCT shows three steps,
24 because the reproducibility -- you're not going to get very
25 many misclassifications by three steps.

1 Now, we're going to talk about clinically
2 significant macular edema in a moment, and just for
3 brevity, I've got it on the same slide, but this four-step
4 scale was reasonably reproducible within one step.

5 Here's a comparison of the eye scale and the
6 person scale. Let's look at the person first. Here is a
7 person with severe NPDR in both eyes. If one of these eyes
8 develops very mild PDR, that's one step on the scale. One
9 of these eyes went to 61, and the other one is still 53.
10 If both of these eyes develop very early PDR, that will be
11 two steps on the scale. That will be 61 on each eye. And
12 if one of these eyes develops more severe proliferative
13 retinopathy, moderate proliferative retinopathy, then we'll
14 go up to three steps, regardless of what the other eye did.

15 Now, it's unusual for one eye to go two steps
16 on the scale and the other eye to lag totally behind. The
17 other eye is usually moving along at least one step. So
18 this less than 65 might be 61 at this point.

19 But at any rate, here are three steps on the
20 person scale, and I think sort of by inspection, one can
21 see that if you had only one eye of this patient to deal
22 with, it would take two steps on the eye scale to get up to
23 this essentially same place. So it sounds complicated, but
24 I think it's very simple. I think two steps on the eye
25 scale is indeed essentially equivalent to three steps on

1 the person scale.

2 Now we get into macular edema, and things are
3 again complex. Here are the ETDRS macular edema
4 definitions. In the ETDRS for eligibility in the trial, we
5 didn't even necessarily require thickening. The principal
6 criterion in the ETDRS was thickening of the retina within
7 one disc diameter of the center, but if the eye had a
8 modest amount of hard exudate, even if we couldn't see
9 thickening, we called it macular edema. I don't think I
10 would do that if we did it over again, but that's what we
11 did. And then we also defined clinically significant
12 macular edema.

13 Dr. Ferris has already gone through this. The
14 mildest variety of clinically significant macular edema was
15 retinal thickening of at least the disc area in extent,
16 some of which was within one disc diameter of the center.
17 The next more severe step in clinically significant macular
18 edema was thickening that was within 500 microns of the
19 center. That's a third of a disc diameter. And then,
20 finally, in the ETDRS analyses, we also did analyses by
21 center involvement, and Dr. Ferris showed you some of those
22 where the center was actually involved.

23 Now, we're proposing as an outcome variable
24 that the center of the macula be involved, and then we're
25 going to back up a little bit from that, definitely

1 involved, retinal thickening or hard exudate involving the
2 center. Well, sometimes it's difficult to tell exactly
3 where the center is, and sometimes it's difficult to tell
4 whether the thickening goes exactly to the center or
5 whether there's a little, teeny bit of thickening or
6 whether there isn't any, so we have a questionably involved
7 level here, which I think is, for practical purposes,
8 involved. And, again, questionably in our scale usually
9 means we think it's true, but we're not sure.

10 Then we back up a little further on this scale,
11 and this is what we would like to define as imminently
12 threatened. The presence of retinal thickening or hard
13 exudate adjacent to retinal thickening almost at the
14 center, within 100 microns from the center, or if there's a
15 plaque of hard exudate, any large accumulation of hard
16 exudate, even if it's not quite so close to the center, we
17 think that's an imminent threat. We also think that in a
18 trial in which patients are admitted with thickening quite
19 some distance from the center, if I, as the clinician
20 following the patient in this trial, see the edge of the
21 macular edema approaching ever closer to the center of the
22 macula, and if I see it move by 1,000 microns, I don't
23 think I'm going to want to withhold photocoagulation any
24 longer. So we would like to include substantial
25 progression of the macular edema as part of the imminent

1 threat.

2 Then up above we merely have a slight
3 modification of the current definition of clinically
4 significant macular edema, in which eyes that just barely
5 meet this definition -- in other words, that are less than
6 500, but not less than 300 from the center -- we would call
7 borderline, and from my point of view, I think such eyes
8 would be eligible for entry into the trial, but then the
9 next step, definite clinically significant macular edema,
10 would not be eligible. So that an eye would have to go
11 from, at most, borderline to, at minimum, imminently
12 threatened, and, again, on this sort of a scale, going from
13 one category to the next category is too subject to
14 misclassification to be a useful outcome. You need to go
15 at least two steps on any of these scales.

16 I think that's my last -- no, I have one more
17 slide, actually. I have one fundus photograph. What I've
18 been saying is a lot of numbers, and I think maybe one
19 picture will help. This is a fundus photograph of a right
20 eye. The optic disc is off the screen to your right. The
21 center of the macula is right about here. You can't see
22 the thickening on this slide. You can see the thickening
23 when you have two photographs on the stereoviewer, but from
24 experience, I'm sure all the retinologists here would agree
25 that we would expect to see thickening inside of this hard

1 exudate ring. The little red spots are hemorrhages and/or
2 microaneurysms. The yellowish white spots are hard exudate
3 lipid deposits. Here's a cotton wool spot, actually. It
4 looks a little different, a little softer. It does look a
5 little bit like cotton.

6 But at any rate, here's the center of the
7 macula, and this amount of hard exudate we're defining as a
8 plaque, a solid area, and that's more of a threat to the
9 center. If that plaque gets into the center, the center
10 won't recover, whereas if the center is just a little bit
11 thickened and we can get rid of the thickening, the center
12 may recover.

13 So here is an eye that we would consider
14 imminently threatened because there's a plaque within 300
15 microns. The posterior edge of this plaque is about 300
16 microns from the center. So there's an example of what we
17 would call imminently threatened.

18 Lloyd?

19 DR. AIELLO: Thank you, Denny.

20 Just by way of a very brief summary now, with
21 the advent of new therapeutic approaches for the treatment
22 of diabetic retinopathy, we presented a series of reasons
23 why we feel that we need to reevaluate the traditional
24 outcome measures for determining efficacy for prevention of
25 proliferative diabetic retinopathy and diabetic macular

1 edema.

2 The specific proposed outcome variable with
3 regard to macular edema is really the only new endpoint
4 that we're proposing, and that is retinal thickening or
5 hard exudate with adjacent retinal thickening involving the
6 center of the macula, and you've heard the rationale why
7 involvement of the center of the macula, we feel, is
8 critical. In addition, due to the fact that there are
9 compelling reasons to treat in some cases prior to
10 involvement of the center of the macula, we are also
11 proposing photocoagulation for macular edema in which the
12 center of the macula is documented to be imminently
13 threatened.

14 You just heard a proposed definition for
15 imminently threatened. Here it is in a smaller manner --
16 that is, retinal thickening or hard exudate with adjacent
17 retinal thickening less than 100 microns from the center of
18 the macula. That is very close to the center of the
19 macula. Or a definite plaque of hard exudate within 300
20 microns of the fovea -- again, here, a plaque, because as
21 Denny told you, this is often more worrisome and, again,
22 relatively close to the center of the fovea. Or
23 development of definite clinically significant macular
24 edema when the posterior edge of the retinal thickening has
25 moved 1,000 or more microns toward the center of the macula

1 as compared with the baseline examination. Here because
2 you have clear progression of the macular edema to a
3 clinically significant point, which is now potentially
4 threatening vision.

5 With regard to the proposed endpoints for
6 proliferative diabetic retinopathy, these are just minor
7 modifications of endpoints that have currently been
8 utilized -- that is, for prevention of documented
9 proliferative diabetic retinopathy, and that should go
10 through a three or more step change on the ETDRS
11 retinopathy person scale if both eyes of the patient are
12 being evaluated, or a two or more step change on the eye
13 scale when only a single eye is being evaluated.

14 Finally, Dr. Ferris mentioned earlier that we
15 may also want to consider for future therapies documented
16 progression of neovascularization elsewhere.

17 Thank you very much for your attention to this
18 presentation, and, of course, at the appropriate time, we'd
19 be happy to answer any questions.

20 Thank you.

21 DR. BONE: Thank you very much to all three of
22 the presenters.

23 We'll take a few minutes here for any questions
24 relating to the presentation -- questions from the
25 committee members, I mean -- and then we'll go ahead with

1 the FDA presentation after any questions by the committee
2 for any of the presenters. Should we just go around the
3 table, I guess?

4 Dr. Feman, do you have any questions for the
5 presenters?

6 DR. FEMAN: Well, I have a series of them. I
7 don't know if this is the correct forum or if I should wait
8 until later for the public discussion, but let me outline
9 some of the --

10 DR. BONE: Can you speak into the microphone?

11 DR. FEMAN: I'm sorry. I have a series of
12 questions. I didn't know if this is an appropriate forum
13 or if I should wait until there's a more broad-based
14 discussion, but --

15 DR. BONE: I would think that at this point
16 we'd want questions related to clarification or factual
17 information or to make sure we're clear about what's
18 actually being proposed, and then for the later session,
19 after we've heard the FDA presentation, sort of broad
20 discussion. So if I can make that distinction, I think
21 that's -- would everyone think that's a reasonable
22 distinction?

23 DR. FEMAN: All right. Then, I will wait until
24 after the FDA presentation.

25 DR. BONE: Very well. Thank you.

1 Dr. Molitch, did you have any specific
2 questions related to the material presented?

3 DR. MOLITCH: I just had one question. I
4 wasn't sure if I made a mistake in hearing what you were
5 presenting or not. Was there a difference in the steps
6 that were outlined for non-proliferative versus
7 proliferative retinopathy? You were saying that you wanted
8 just the single eye measurement of two steps for the non-
9 proliferative, and for proliferative it could either be the
10 two steps in a single eye or three steps per person. It
11 looked like it was an either/or for proliferative and not
12 an either/or for the non-proliferative, or was I mistaken?

13 DR. DAVIS: How crucial is it that I use a
14 microphone?

15 DR. BONE: Very. Please step up to a
16 microphone. You can use one of the ones at the table.

17 DR. DAVIS: Okay. This will be a quick answer.

18 DR. BONE: This is Dr. Davis.

19 DR. DAVIS: Matthew Davis speaking. We did not
20 mean to distinguish between proliferative and non-
21 proliferative. I just happened to use the example because
22 we're thinking about agents that may prevent or slow
23 progression to proliferative retinopathy.

24 DR. MOLITCH: So it's either/or for both.

25 DR. DAVIS: Either/or for all parts of the

1 scale.

2 DR. BONE: Other questions, Dr. Molitch?

3 DR. MOLITCH: No.

4 DR. BONE: Dr. Spellman?

5 DR. SPELLMAN: No.

6 DR. BONE: Dr. Zawadzki?

7 DR. ZAWADZKI: The diabetes control and
8 complications trial showed an improvement in retinopathy.
9 Was there also an improvement in macular edema in the
10 intensively controlled group?

11 DR. BONE: Dr. Ferris is responding.

12 DR. FERRIS: There was a difference in macular
13 edema. It actually wasn't as big as some of the other
14 differences that were demonstrated with regard to
15 retinopathy, and it was not statistically significant, the
16 rate to macular edema, but there was a difference.

17 DR. BONE: By "not significant statistically,"
18 do you mean there was a trend?

19 DR. FERRIS: Well, there was a strong trend,
20 but the relative risk was smaller for macular edema than
21 for others, and it's a matter of how you look at it,
22 whether you would call it statistically significant or not.
23 I probably am a stricter -- since it wasn't a primary
24 outcome variable, I would like to see a stronger level of
25 statistical significance. But I think from a clinical

1 point of view and from a sensible point of view, you would
2 say that tight control does affect macular edema, and tight
3 control in any of these, I think, has to be considered as a
4 confounding variable. You need to make sure that both
5 groups have relatively equal control if you're going to
6 look at progression of retinopathy as an outcome variable.

7 DR. BONE: Thank you, Dr. Ferris.

8 Dr. Zawadzki, any further questions or
9 anything?

10 DR. ZAWADZKI: No.

11 DR. BONE: This would be Dr. Sloan Wilson.

12 DR. SLOAN WILSON: Not at this time, thank you.

13 DR. BONE: Dr. Seddon?

14 DR. SEDDON: Just a question about the
15 secondary outcomes. Is there still consideration for using
16 photocoagulation for documented PDR? Will there be
17 secondary outcome discussions or -- I was a little confused
18 about that. And the other is the documented progression of
19 NDE. I know you didn't want those to be primary outcomes,
20 but will they be secondary outcomes?

21 DR. BONE: This is Dr. Ferris.

22 DR. FERRIS: I think we believe that as a
23 primary outcome variable, the least affected by the
24 potential for bias is documented progression prior to
25 photocoagulation. Inevitably, in a study there will be

1 people who receive photocoagulation, but either you didn't
2 get the pictures or the pictures didn't document the change
3 that the clinician thought existed and they didn't wait to
4 get verification that progression had occurred. And they
5 may not be able to wait. There are lots of patient-related
6 issues where, if you're going to keep the patient in the
7 trial, you have to accede to some degree of wishes.

8 I find photocoagulation in that case, where you
9 could not document progression, to be a useful secondary
10 outcome variable. I have a problem with it as a primary
11 outcome variable. That's why we're trying to differentiate
12 here between documented progression with photocoagulation
13 and photocoagulation without documented progression.

14 DR. SEDDON: So they will be considered
15 secondary outcomes?

16 DR. FERRIS: In my view, like visual acuity,
17 it's a bad thing for the patient. If they lose vision or
18 if they have photocoagulation, then they need to be counted
19 and they need to be presented. My view about presentations
20 or studies where you say, "This is my outcome variable,"
21 well, that's interesting, but you need to look at other
22 things, such as the side effects and other outcome
23 variables, to make sure that they're consistent with what
24 you're claiming based on one single outcome variable.

25 DR. BONE: Anything further, Dr. Seddon?

1 DR. SEDDON: No.

2 DR. BONE: Thank you.

3 Dr. Roy Wilson?

4 DR. ROY WILSON: No questions.

5 DR. BONE: And Dr. Jose Cara has joined us.

6 DR. CARA: I think I need some clarification in
7 terms of the element of time in this, and my question
8 relates to the fact that in diabetic ophthalmopathy, it's
9 not unusual to see a transient worsening of ophthalmopathy
10 with a more aggressive therapy. How do you take that into
11 account? What degree of worsening is considered a stopping
12 point for therapy, and what minimum course of time is
13 necessary before you can really evaluate some of these
14 outcomes?

15 DR. FERRIS: This is Rick Ferris again. I
16 think any of us could answer this. Time is a critically
17 important issue with regard to this. We think that a
18 three-step change on this scale or the development of
19 proliferative retinopathy or having the center of the
20 macula involved is a bad outcome for the patient. These
21 changes, on average -- for example, looking at the ETDRS
22 data, to do a clinical trial of diabetic macular edema and
23 to have a reasonable number of events, outcomes, if you
24 start with patients who have a little edema, but not
25 important edema yet, would be over the course of several

1 years, I think, at a minimum. So that we need to follow
2 these variables for at least that amount of time.

3 One of the reasons that we want to look at
4 these variables or that we're proposing these variables
5 relates, I think, directly to the time issue. If we had to
6 do a clinical trial of proliferative diabetic retinopathy
7 and were forced to use what we were able to use in the
8 diabetic retinopathy study -- and that is severe visual
9 loss as an outcome, which everybody would agree to -- and
10 you needed at least two doses of a new treatment, which I
11 believe is what the FDA is asking for, the sample size
12 would be roughly 26,000 patients followed for 5 or more
13 years. Well, that will have a chilling effect on any new
14 treatments for proliferative diabetic retinopathy, because
15 I don't know any company that would have the wherewithal to
16 initiate that kind of trial.

17 For diabetic macular edema, if we were forced
18 to use a three-line change of visual acuity, doubling of
19 the visual angle, as the outcome variable, our estimates
20 are it would be a several-thousand-patient trial followed
21 for at least 3 years, with the caveat that I am unwilling
22 to use visual acuity alone as an outcome variable, because
23 I'm afraid that photocoagulation may be differentially
24 applied.

25 I don't know if that directly answers your

1 question.

2 DR. CARA: It gives me an idea. Thanks.

3 DR. BONE: Dr. Mindel?

4 DR. MINDEL: It has to do with your answer to
5 the last question. The number of patients that would be
6 needed, if you used visual acuity, would be several
7 thousand?

8 DR. FERRIS: Yes. I can give you the specific
9 numbers that I used to --

10 DR. MINDEL: Yes, I'd be interested in knowing
11 that.

12 DR. FERRIS: I'm afraid you'll have to give me
13 a second to actually -- and, unfortunately, I need to take
14 my glasses off.

15 For scatter photocoagulation, given the rates
16 that we see after photocoagulation in the ETDRS, using 80
17 percent power to find a 30 percent difference over a 3-year
18 study would require 7,286 patients in each of three study
19 arms. For a 5-year study, you could reduce that down to
20 8,500 patients. For macular edema, what we used was a 12
21 percent 3-year rate, which was what we saw in the treated
22 eyes in the ETDRS.

23 DR. BONE: Possibly if we could come back to --

24 DR. FERRIS: Yes, why don't you go ahead and --

25 DR. BONE: If Dr. Mindel's agreeable, we could

1 probably get this after the break, this figure.

2 DR. MINDEL: Yes, okay.

3 DR. BONE: I think that's going to be the most
4 efficient thing to do, and we'll get the information, I'm
5 sure.

6 Dr. Davidson?

7 DR. DAVIDSON: Well, it's the same. You know,
8 if I'm a patient, I'm not concerned about how many steps,
9 but if I'm going to be blind or not -- and I think
10 blindness should be a primary endpoint. Unless we have
11 that, can we prove that it's cost efficient? In Texas, for
12 example, we have more than 2,000 new cases of blindness
13 from diabetes each year, and it costs the state about
14 \$77,000 to rehabilitate these people. If a treatment is
15 good just to prevent step changes, but at the end patients
16 are going to be blind, as a consumer for this group, I'm a
17 little bit concerned if blindness is not a primary
18 endpoint.

19 DR. BONE: Dr. Freeman apparently has a comment
20 or response to Dr. Davidson's comment.

21 DR. FREEMAN: I think the problem is that
22 blindness, as I read through the information that we were
23 given, is quite uncommon, given the other therapies that
24 are available. So I think we have to look at other
25 endpoints or actually -- and maybe I'll take my turn now.

1 My question -- and certainly the people
2 presenting to us know this data very well -- there are
3 other measures of vision. There are tests of reading and
4 reading speed, and we've used those in clinical trials of
5 macular hole surgery and of the ability to see contrast,
6 and perhaps those are being considered or should be in the
7 visual outcome. That might help really get a better
8 picture of vision. Photocoagulation, for example, in the
9 macula may reduce contrast, may affect reading speed, and
10 those outcomes are real outcomes for patients and can be
11 measured.

12 DR. BONE: Do you want to respond to that, Dr.
13 Ferris?

14 DR. FERRIS: Yes. We, of course, agree that
15 you need to look at visual function, visual acuity first,
16 contrast sensitivity, other things as well. I would
17 emphasize that the main reason people are going blind in
18 Texas and in the United States and in the world from
19 diabetic retinopathy is because they're not getting
20 photocoagulation, not because we don't have effective
21 treatments. However, I believe, particularly for macular
22 edema, but also for proliferative retinopathy, that we
23 could do better, and the only way to do better is to try to
24 find new treatments.

25 I found the numbers, by the way, if they would

1 be useful.

2 DR. BONE: This is in response to Dr. Mindel's
3 question?

4 DR. FERRIS: Right. Actually, using a 15
5 percent event rate in treated eyes, which --

6 DR. BONE: This is for macular edema?

7 DR. FERRIS: For macular edema. This is a
8 visual acuity loss outcome. Fifteen percent over 3 years
9 would be projected to have a doubling of the visual angle.
10 To find a 30 percent reduction in that would require a 3-
11 year study of 1,472 patients in each of three study arms,
12 and that's a total of 4,416 patients.

13 DR. BONE: Dr. Mindel?

14 DR. MINDEL: You said treated patients. Would
15 you tell me what you mean by -- you're starting with
16 treated patients in this analysis?

17 DR. FERRIS: No. If you took -- actually, this
18 would be a best case, because this is taking people who are
19 likely to need treatment. This is using the ETDRS patient
20 group as a starting point, which would probably be more
21 severe than the kind of starting point that you would be
22 able to use in a study looking, as we're suggesting, for
23 progression of macular edema to involve the center. In the
24 ETDRS, the event rate was 15 percent.

25 The reason that you have to count treatment is

1 that you cannot withhold photocoagulation from patients who
2 develop macular edema that involves the center. It's
3 outside of the standard of care. It might be good for the
4 clinical trial, but I wouldn't be willing to do it.

5 DR. MINDEL: I want to get back, though, to the
6 frequency. I'm still not sure -- you're saying all the
7 patients enrolled into the study you're using?

8 DR. FERRIS: No.

9 DR. MINDEL: You said that you were qualifying
10 it by saying these are more likely to develop macular edema
11 than others, and I don't quite understand that, either.

12 DR. FERRIS: Well, if you were evaluating a
13 treatment for diabetic macular edema, you would tend to
14 enroll patients who you thought were at reasonably high
15 risk of having macular edema during the study period. For
16 example, the patients that we would consider for a new drug
17 would be patients who had some macular edema in the
18 posterior pole, but not yet threatening the fovea. So we
19 view this as a group of patients who are at fairly high
20 risk to progress, but who at this point do not need
21 photocoagulation. And what we're trying to do is get
22 photocoagulation out of this as a confounding variable, so
23 we're trying to see the effect of the drug prior to the
24 need for photocoagulation, because I think photocoagulation
25 itself is something that you would like to avoid if you

1 could, that there's value in doing that.

2 I agree that we need to look at visual acuity,
3 too, of course, because let's say you have a new drug that
4 causes cataract. You have to look at visual acuity,
5 because you have to look at that as, I think, the most
6 sensitive measure of the side effects of treatments in the
7 eye, and Dr. Freeman, of course, is right that other
8 functional -- visual acuity is not the only functional
9 parameter that is of interest.

10 DR. MINDEL: So the number of patients you
11 think you would need to do a study if you used visual
12 acuity would be? For the macula.

13 DR. FERRIS: For the macula, the minimum number
14 is 4,416, and I view that as -- the 15 percent event rate,
15 given photocoagulation, I think is probably overly
16 generous. I think that we probably do better than that,
17 and I think if you start with this group that's defined as
18 having more peripheral macular edema, their rate is going
19 to be lower than the rate that we observed in the ETDRS,
20 where we had probably, on the average, a more severe group
21 of patients.

22 The other thing with regard to the sample size
23 that I would point out, when we went from the DRS to the
24 ETDRS and we used our estimates of the event rate of bad
25 outcome from the DRS, what we found was that we were off by

1 more than a factor of two, because as photocoagulation
2 became more incorporated into general treatment, I think
3 the ophthalmologists did better and the rates of the bad
4 outcome actually went down. The treated eye rates were
5 remarkably down.

6 DR. BONE: Dr. Ferris, in further to this,
7 you're using what for the power for that calculation?

8 DR. FERRIS: Eighty percent.

9 DR. BONE: And if you use 90 percent, which
10 would be a little more conservative from the standpoint of
11 trial design?

12 DR. FERRIS: You're way over 5,000 patients.

13 DR. BONE: Per arm.

14 DR. FERRIS: No, for the total study. I didn't
15 do it for --

16 DR. BONE: It would probably at least double
17 the sample size, wouldn't it?

18 DR. FERRIS: Well, it's going to be, yes,
19 between 50 percent and double, the increase.

20 DR. BONE: All right.

21 Anything further, Dr. Mindel?

22 DR. MINDEL: No.

23 DR. BONE: Dr. Carney?

24 DR. CARNEY: I just have one question about the
25 consideration. When you were talking about the

1 consideration of documented progression, would it be of or
2 to neovascularization elsewhere?

3 DR. FERRIS: Oh, this is this other outcome
4 variable? For example, for anti-angiogenic treatments, the
5 proposal there would be that you -- I mean, one approach
6 for an anti-angiogenic drug would be to start as a
7 preventative treatment, and for that we think we've got
8 that covered. But others might say if you had
9 neovascularization and you had a drug that might make
10 neovascularization go away, I would like to test that drug,
11 and what we're saying is that a change in the amount of
12 neovascularization may be a useful outcome variable. I
13 think you'd have to document, as we've done for these step
14 changes, what the reproducibility is, and I think you'd
15 have to show that you have probably something like a 90
16 percent chance of not making a false-positive error in
17 saying that a change has occurred when it has not really
18 occurred.

19 So the concept there is that that would be the
20 kind of outcome variable that we would like to see. It
21 hasn't been used before, so we haven't fleshed it out quite
22 as well as these other outcome variables have been fleshed
23 out, but I would think that a method of comparing base line
24 with follow-up and a definite either progression or
25 regression of neovascularization would be a useful outcome

1 variable for our study.

2 DR. BONE: But that's not a proposal at the
3 moment. It's not a specific proposal.

4 DR. FERRIS: It's not necessarily a specific
5 proposal, because I don't know of any drug that is
6 currently being proposed for that, but I think it's worth
7 reviewing if this is a general discussion of outcome
8 variables for diabetic retinopathy, because there will be
9 drugs that will be proposed for that.

10 DR. BONE: I see. The chair has a couple of
11 questions. One has to do with this use of single eyes, and
12 you'll forgive me, I think I'm the only one here who's
13 neither a diabetologist nor an ophthalmologist, so I'm
14 permitted, I think, to ask naive and other sorts of
15 questions that perhaps other people would be interested in
16 as well. How big a problem would it be just to not use
17 patients who have only one evaluable eye? Obviously, you
18 could just exclude these patients from the trial, and it's
19 a sort of practical problem, it seems to me, and I guess my
20 question is, is this a big practical problem or just a
21 little practical problem?

22 DR. FERRIS: My view is that it's potentially a
23 big practical problem, and the area where I think it's a
24 big practical problem relates particularly to Type II
25 diabetics who have severe non-proliferative retinopathy.

1 We've done some data analysis, which I think a lot of the
2 panel members know, which suggests that for them earlier
3 treatment may be particularly beneficial, that deferring
4 treatment may be a problem. Well, this suggests that this
5 group of patients may well wind up with treatment prior to
6 proliferative diabetic retinopathy in at least one eye.

7 I personally would be happy to take a patient
8 like that and do early treatment in one eye and defer the
9 other eye until I actually saw neovascularization. I would
10 be unhappy about entering such a patient if I were
11 essentially required to wait until proliferative
12 retinopathy developed in an eye to even treat one of the
13 patient's eyes.

14 The other thing is that a lot of patients also
15 have fairly asymmetric retinopathy and will have had
16 photocoagulation in one eye already. Once an eye has been
17 photocoagulated, I think with regard to these treatments,
18 the confounding effect of photocoagulation is so strong
19 that using it as a primary outcome would be a significant
20 problem.

21 DR. BONE: So you're talking about where the
22 other eye has been treated prior to study entry, not
23 continuing to evaluate the patient's remaining eye that
24 hasn't been photocoagulated in an ongoing way. In other
25 words, that patient, once they've reached photocoagulation

1 and if both eyes were untreated to begin with, would have
2 reached endpoint. You're not talking about continuing to
3 evaluate the eyes separately after a patient has been
4 treated on study?

5 DR. FERRIS: What we're proposing is that for
6 patients who have had an eye treated, that they be allowed
7 to enter the study and that the study eye be identified at
8 the beginning that this is a patient that we're only going
9 to follow one eye and this is the eye we're going to
10 follow, and you identify it from the beginning, and that's
11 the eye you follow, and what happens to the other eye may
12 be in some secondary analyses used, but it's not the
13 primary.

14 DR. BONE: Because you're not talking about
15 continuing to evaluate the other eye after the first eye
16 has been treated during the study.

17 DR. FERRIS: No. Of course, I follow all eyes
18 in every patient.

19 DR. BONE: Yes, but I mean as far as -- okay.
20 Very good.

21 Yes? This is Dr. Feman.

22 DR. FEMAN: Dr. Feman. I have a concern
23 because although we've all made an assumption that treating
24 one eye does not influence the other eye, I don't know of
25 good, hard data that says that treatment of one eye does

1 not have an effect on the fellow eye of the patient. There
2 may be such data, but I'm not familiar with it.

3 Is there anything in the literature now that
4 says that if you treat one eye, the patient will not have
5 an effect on their other eye by the treatment on the first
6 eye? Will the patient change their overall means of
7 controlling their diabetes perhaps because they've already
8 had laser surgery on one eye, or could there possibly be an
9 effect of the treatment on one eye crossing to the other
10 eye in some way? We've all made an assumption that that
11 doesn't happen, but we don't know that.

12 DR. FERRIS: Well, there are lots of potential
13 confounding variables that we both know and don't know.
14 Tightness of control, for example, is a confounder that you
15 can control for and you can analyze. You can also analyze
16 for progression in one-eyed patients versus progression in
17 two-eyed patients, and it's a randomized -- at least I
18 think it needs to be a randomized design, and if you have a
19 randomized design, you've got the power at least to address
20 the question as to whether the one-eyed patients did
21 differently.

22 If these are one-eyed patients that had already
23 had photocoagulation in the other eye, the distant effect
24 of photocoagulation might be an interesting possibility,
25 but I would suggest there might be another problem, and

1 that is that those patients may be more likely to progress
2 because they have more severe retinopathy to start with, so
3 that their progression rates indeed might be somewhat
4 different, and just as you would have to control for
5 hemoglobin A1C levels to make sure that randomization
6 worked, you'd have to make sure that randomization worked
7 with regard to one-eyed patients and two-eyed patients.

8 DR. BONE: Dr. Feman, is there anything
9 further?

10 DR. FEMAN: Well, it's just that in all the
11 studies that I'm aware of in which there is data for one
12 eye progression, that happened to be in individuals in whom
13 two eyes were present, and they were just doing an analysis
14 of one eye. It wasn't individuals that had one eye treated
15 with a different modality and the first eye was treated
16 with still another modality.

17 So there's no study that I'm aware of, except
18 for perhaps the early diabetic retinopathy study, where you
19 have statistical data for one eye treatment and the other
20 eye not getting treatment in the same individual.

21 DR. BONE: So, presumably, that would have to
22 be allowed for in the trial design, but we wouldn't have to
23 answer the question in order to design the trial,
24 presumably.

25 I have one other question here, and, again, I'm

1 probably the most naive member of the group here about some
2 of these issues, but it seems to me that we're proposing a
3 change, and I'm not as clear as I guess I could be about
4 what we're proposing a change from. The suggested
5 endpoints, I think, have been fairly clearly articulated,
6 but are you proposing to change from the early retinopathy
7 studies that you described, or are we talking about a
8 change from some other set of criteria? I mean, since we
9 haven't actually brought a drug to evaluation here, I'm not
10 sure what the bench mark is for criteria for efficacy.
11 Could you kind of explain to me how that compares?

12 DR. FERRIS: Well, I think there is no bench
13 mark for the FDA looking at outcome variables for diabetic
14 retinopathy, because -- and maybe one of you can correct
15 me, but I don't know of any that have come using any of
16 these outcome variables. There are plenty of studies that
17 have come using visual acuity as an outcome variable, and I
18 believe there's an agreement that a three-line change on
19 the ETDRS-type chart would be considered a primary outcome
20 variable of definite importance.

21 What we're proposing is that visual acuity
22 becomes a problem in the face of the confounding of
23 photocoagulation, and that's why we're saying that we can't
24 evaluate new drugs if we're required to use visual acuity
25 as the primary outcome variable, both because of the

1 difficulties in size and cost, but equally or more
2 important because of the potential for confounding and
3 bias. So we are coming to propose variables for study in
4 advance of treatments being tested to get guidance for
5 companies that might have new treatments with regard to
6 what a committee such as this would consider clinically
7 important outcome variables for which there could be an NDA
8 approved.

9 DR. BONE: So let me see if I'm putting this
10 together correctly. You're saying that most of the
11 precedents are really for the use of visual function as
12 endpoints, and you're proposing that since the changes in
13 visual function are late and may also be confounded by
14 other interventions that would be required by the standard
15 of care, that one might use the anatomic pathology of the
16 disease as a measure of progression or response to therapy.

17 DR. FERRIS: That's right. There was a meeting
18 in the 1980s of a similar panel to review the steps of
19 progression of retinopathy as a potential "surrogate" for
20 bad outcome, and I think there was agreement at that
21 meeting, if I read the minutes correctly, that a three-step
22 change on that scale that we presented would be viewed as a
23 clinically important bad outcome for a patient. The DCCT
24 didn't have to come to the FDA to get its results approved,
25 but I think that if it had been a drug rather than

1 tightening of blood sugar, a proposal could have come using
2 that.

3 So we're not suggesting we change that. We
4 would like to get sort of validation that that kind of
5 progression would be considered by a committee such as this
6 as an important outcome variable, and we would like --
7 because photocoagulation has now entered the scene and is
8 so effective at reducing the risk of visual acuity, for
9 that reason we think that we need to use some other outcome
10 variables in addition to visual acuity.

11 As I said, I think if visual acuity is going
12 one direction and these anatomic changes are going the
13 other, it wouldn't get past me if I were sitting on the
14 panel, because I agree with the comment that the thing
15 that's important to the patient is their visual acuity.
16 But it's important down the road, too, and what we were
17 trying to do was to show that these outcome variables are
18 important to the patient in and of themselves,
19 photocoagulation is an important outcome in and of itself
20 to the patient, and we think that it reduces the risk of
21 vision loss.

22 DR. BONE: So anatomic changes and
23 interventions in addition to functional loss would be the
24 differences.

25 DR. FERRIS: Yes.

1 DR. BONE: We've got a couple more comments,
2 and then we'll go on to Dr. Chambers.

3 Dr. Chambers, did you have a question?

4 DR. CHAMBERS: Just a clarification. I will go
5 through, in my presentation, endpoints that the agency has
6 already said in the past we would take as definitive
7 endpoints.

8 DR. BONE: Great. That will be very helpful to
9 this.

10 Okay. Dr. Mindel, Dr. Cara, and then we'll go
11 -- oh, and Dr. Feman.

12 Dr. Mindel?

13 DR. MINDEL: Regarding just macular edema, why
14 should we use the ETDRS criteria at all for evaluating the
15 macula? It seems we're using 1968 state-of-the-art
16 techniques inappropriately when that study was to compare
17 the natural course of the disease with a specific
18 treatment, laser photocoagulation, and you had to use
19 something that was appropriate for clinical intervention.
20 Why apply that or is it appropriate to apply that to a drug
21 study?

22 What's making this study burdensome is your
23 criteria. I'm not certain -- I'm just talking about
24 macular edema. For macular edema, it seems that this is
25 somewhat self-serving in a way even. Why should we involve

1 those criteria at all? What's the justification when you
2 make this presentation for using them?

3 DR. FERRIS: Well, my justification would be
4 that this was the research that we did in the 1980s and
5 1990s. These criteria were developed in the mid-1980s. To
6 my knowledge, I don't know of any other descriptive
7 criteria that have been so well studied and validated. We
8 present these because we have data that shows that we can
9 use them in a way that is reliable.

10 That's not to say that there won't be new
11 things that would be better outcome variables. For
12 example, retinal thickness analyzers are being developed
13 and so on. They may become, in my opinion, reliable.
14 They're not now reliable enough to use as a major outcome
15 variable for a clinical trial. That's why we're not
16 proposing those.

17 DR. MINDEL: I don't want to carry this any
18 further, because I think it's getting away from
19 clarification, but how reliable your criteria are is really
20 very debatable. When you took how good the agreement was
21 between two observers and what the level of difference was
22 in terms of the criteria, the steps -- what I'm worried
23 about is, we're going to be locked in by making -- you
24 know, we're talking about ongoing studies now for the
25 future -- whether we're going to be locked in to 1968

1 criteria. As you said, there are at least two other
2 techniques that hold a lot more promise than non-
3 simultaneous stereophotographs, and I think that should be
4 also in the back of our minds when we evaluate these
5 criteria.

6 DR. BONE: Well, then, maybe what we can do is
7 perhaps have a little time later in the day for a
8 discussion of how the question of macular edema might be
9 evaluated technically, but I think the first issue seems to
10 be more the question of whether an anatomical evaluation of
11 macular edema is the appropriate endpoint, and then the
12 next question would be the one for the experts to grapple
13 with about how best to do that. So it's kind of a two-step
14 issue, it seems to me.

15 Let's see, I think Dr. Cara and then Dr. Feman
16 had questions.

17 DR. CARA: I don't want to take anything for
18 granted. I take it that these outcome variables that
19 you're proposing are geared toward treatments that involve
20 both local therapy to the eye as well as systemic therapy
21 to the individual.

22 DR. FERRIS: Yes, and we use these outcome
23 variables -- if you read, for example, the American Academy
24 of Ophthalmology Preferred Practice Plan, they use these
25 variables of center involvement and degree of thickening as

1 the guidelines for photocoagulation. So we may do better
2 in the future, but these are the ones that are part of
3 current practice. The only difference between practice and
4 the study is that we're using photographs as a way of
5 documenting this rather than just using the clinician's
6 opinion.

7 DR. CARA: The other question is, have you
8 developed any fail-safe mechanisms that would allow -- I
9 don't know if suspension is the right word, but at least
10 discontinuation of the trial based on unexpected
11 progression of diabetic ophthalmopathy?

12 DR. FERRIS: The answer is that, for example,
13 in our collaboration with Eli Lilly, the role that the
14 National Eye Institute is playing is in trying to help with
15 the study design, to be involved. Perhaps it's good for
16 Lilly and I assume it's good for others if we can come to
17 some outcome variables that people can use in other
18 studies.

19 DR. CARA: Well, that really doesn't address
20 the question.

21 DR. FERRIS: I'm sorry. Say the question
22 again.

23 DR. CARA: What I'm concerned about is the
24 potential worsening of diabetic ophthalmopathy with
25 specific interventions.

1 DR. FERRIS: Are you talking about stopping
2 rules?

3 DR. CARA: The case that comes to mind is the
4 proposed IGF-1 therapy for diabetes, and that trial was
5 suspended because of the inordinate progression of the
6 ophthalmopathy, which really wasn't quite expected.

7 DR. FERRIS: What I was -- I didn't finish my
8 thought and lost it somehow. First time that ever
9 happened.

10 (Laughter.)

11 DR. FERRIS: The National Eye Institute's role
12 is to also choose a data monitoring committee, have it meet
13 regularly the way all of our data monitoring committees do,
14 to look specifically for either early benefits or early
15 harms from treatment.

16 DR. CARA: Wouldn't it be advantageous to have
17 specific guidelines, however, that would serve as a fail-
18 safe mechanism?

19 DR. FERRIS: For worsening? Well, I guess
20 we're proposing that these outcome variables can be used
21 both ways, that they can be looked at for benefit, but they
22 can also be looked at for worsening. If the treated group
23 starts losing visual acuity, for example, that would be a
24 concern to a data monitoring committee. If the treated
25 group has more macular edema, that would be a concern. The

1 outcome variables that we know how to use are the ones that
2 we presented. We would hope to use some of these other
3 outcome variables in addition as secondary outcome
4 variables that would be used to monitor side effects as
5 well as beneficial ones.

6 DR. CARA: Well, maybe in the discussion we can
7 address that issue further.

8 DR. BONE: I think that's a trial design issue,
9 not necessarily an endpoint. It's a different kind of --

10 DR. CARA: No, it's an endpoint.

11 DR. BONE: Well, it's how to use an endpoint.

12 Dr. Feman, and then we'll --

13 DR. FEMAN: Correct, this is Dr. Feman again.
14 The only other question I had was -- and I wasn't aware
15 until I heard the other discussions -- I was not aware of
16 how many people in the audience and in the panel have not
17 devoted their careers to looking at diabetic retinopathy
18 specifically. This step-wise pattern that we're using,
19 many of you may not be aware of, is not really a linear
20 range, and it's probably not even a logarithmic range, that
21 when an eye goes from, say, 43 to perhaps 50 is not the
22 same as an eye going from, say, 53 to 67. These steps
23 really are just their worsening, but how much worsening is
24 just an arbitrary number. For example, a 43 to a 47 is not
25 the same as a 61 to a 65, and if we're using this step-wise

1 system, we need to be aware that these steps are not all
2 equal.

3 DR. BONE: Thank you for that comment.

4 I think the suggestion was made that we go
5 ahead and take the break early. Is that acceptable, Dr.
6 Chambers? Then we'll return at -- I have 10:12, and we'll
7 resume at 10:30, and we may move up the open public
8 session, depending on the time, too, making it before
9 lunch.

10 (Recess.)

11 DR. BONE: We're resuming the joint committee
12 meeting on diabetic retinopathy clinical trial endpoints.
13 The next presentation will be by Dr. Wiley Chambers of the
14 Food and Drug Administration.

15 Dr. Chambers?

16 DR. CHAMBERS: Thank you.

17 What I would like to do first is go through a
18 number of the issues which I can identify in the
19 literature, which are probably relatively well known to
20 everybody, but which have been causing the members of my
21 staff difficulty in coming up with specific endpoints.
22 Most of the issues that I've identified, I tried to put in
23 the background that I sent out a single reference in the
24 literature that identified this particular problem. In
25 most cases, you can find other literature articles that are

1 directly 180 percent contrary to the statement that I put
2 in the background, and this was not meant to state that
3 this is the only opinion, and as I go through these, this
4 is not the only opinion, but it's the fact that there is
5 controversy in this area.

6 The first is that the pathogenesis of diabetic
7 macular edema and diabetic retinopathy is not completely
8 understood. If we understood exactly how everything works,
9 we probably would have a much easier time. But because we
10 are just observing different factors, we don't know how to
11 predict every step along the way. And, unfortunately, the
12 risk factors may be different based on different stages of
13 retinopathy. Literature reports have stated that the risk
14 factors for PDR may be different than that for non-
15 proliferative diabetic retinopathy, and there is some
16 question about whether even the risk factors within
17 proliferative diabetic retinopathy, comparing early
18 diabetic retinopathy and severe proliferative diabetic
19 retinopathy, are the same, and there is at least one report
20 that the time to non-proliferative diabetic retinopathy is
21 inversely correlated with the development of proliferative
22 diabetic retinopathy. That raises the question whether
23 other phenomena are just going on and whether the ultimate
24 outcome -- i.e., preventing blindness or preventing visual
25 loss -- can be just fooled by having different endpoints

1 showing up at different stages.

2 There are multiple classification systems used.
3 I do want to thank the earlier speakers for presenting a
4 great deal of the background so that I did not have to go
5 into a lot of the scales that are used. But as they had
6 pointed out, even the scales that are currently being used
7 are not the same ones that were used. They're based on
8 earlier scales, but they have been modified as we've
9 learned more. It is to their credit that they've modified
10 the scales as they've seen different things, but there are
11 different scales, and the group that presented earlier is
12 not the only system that is currently available.

13 From the Food and Drug Administration's point
14 of view, not having a single gold standard is potentially a
15 problem, because we would not direct anybody to a
16 proprietary system or a single system. We would generally
17 try to allow anything that's scientifically sound to be
18 used. Because there are multiple systems, different
19 sponsors of different applications may disagree on what the
20 best system is. Individual investigators within a trial
21 may have the choice of either enrolling patients in the
22 trial or not enrolling patients in the trial if they
23 disagree, but, again, the problem occurs because we don't
24 have a single system. And I don't know that we necessarily
25 have to have a single system, but it makes recommendations

1 more difficult.

2 As has been mentioned earlier, the current
3 classification scales do not have equal spacing between
4 steps, so when we talk about doing two-step changes, three-
5 step changes, or a one-step change, depending on where you
6 are in the scale may have a big impact on that. And I'm
7 not sure that it's easy. I mean, at the moment we can't
8 even say that it's a linear scale or a logarithmic scale,
9 but the steps are just markers of different points of
10 progression.

11 One of the factors that hasn't been talked
12 about yet is, if the drug product that's being tested
13 alters the natural course, then the information we have to
14 date about what the normal steps that we would expect
15 people to go through in diabetic retinopathy may not hold
16 up. It's entirely possible that some of the signs and
17 symptoms that we typically see may not occur with a
18 particular drug product, because they may inhibit those
19 particular steps. That may be beneficial, but it may also
20 be harmful or we may believe just because we've stopped one
21 step that the steps later on may still occur, and if that
22 occurs, how do we know we haven't just fooled ourselves by
23 not seeing a particular pathogenesis or a particular step?

24 The other possibility that has been discussed a
25 couple of different times is that some of our current

1 therapies, such as PRP, may interfere with the normal
2 progression or may interfere with our ability to observe
3 particular endpoints. If we don't permit these therapies
4 to occur, then we may potentially delay therapeutic avenues
5 for these patients. On the other hand, if the therapies
6 are permitted, it may be difficult to establish which
7 therapy was causing which effect.

8 The clinical signs and symptoms, unfortunately,
9 are not always constant. Things like microaneurysms might
10 not be visible throughout the whole period of time. Once
11 you get a microaneurysm, you don't necessarily continue to
12 have that microaneurysm. They've been observed to
13 disappear or at least not be clearly visible. Hemorrhages
14 obviously will come and go as the body heals them. The
15 optimal time that was brought up earlier has not been
16 established for many of these events, and while we're
17 talking about the potential for some trials going on 3, 4,
18 5, 10 years, in most cases trying to evaluate drug
19 therapies and have a consistent clinical trial throughout
20 that whole period of time and have patients stay in that
21 trial during that time is difficult.

22 Diabetic macular edema can spontaneously be
23 resolved, and in one of the literature reports -- actually,
24 in a couple of the literature reports approximately a third
25 of patients have had it resolve in 6 months. Now, if the

1 condition is going to resolve by itself in 6 months in a
2 third of patients, that's a relatively high percentage of
3 people. Yes, that's two-thirds where it didn't go away and
4 potentially could be harmful, but it has impact on the
5 overall numbers of patients that are necessary because of
6 the variability and how long does an event have to still be
7 there. I mean, should we not be saying that these are
8 events that occur at one point, but should they always be
9 events that we see now and also the same event 6 months
10 later or 3 months later or 1 year later? But those types
11 of questions need may need to get plugged into endpoints.

12 Among the biggest potential confounding factors
13 has to do with what was observed in the DCCT trial. If
14 anyone were to look at the results 1 year out, 2 years out,
15 the answer that you would come up with from the DCCT trial
16 is not the same answer that you would come up with looking
17 at those results 5 years out, and the agency is
18 particularly concerned about not being fooled that an early
19 change is not the same as what happens later on.

20 Now, there are a number of reasons that people
21 believe this occurred, and we believe now that we could go
22 and catch that, whether it's reflective of particular types
23 of patients that got enrolled and what the particular
24 endpoints that were being looked at were. But it is a
25 concern, and we now retrospectively think we can understand

1 what was happening, but it was not the same as when the
2 trial was going on, and if we were to repeat that same type
3 of event just with slightly different findings, would we be
4 able to recognize it now, or would we only recognize it 10
5 years from now?

6 The types of treatments that the agency is
7 interested in ultimately approving would be things that
8 clinicians could identify as being useful for their
9 patients, which means they need to be able to have
10 endpoints that they can look at their patients and
11 recognize, "This is a patient I would then use that therapy
12 for." It has to go back to how we would label a particular
13 drug product. It's true that we've had many trials where
14 the particular -- because the control necessary in the
15 clinical trial is not exactly the same in the clinical
16 trial as is in clinical practice, there needs to be some
17 way of making that correlation and some way of identifying
18 the group of patients for which a therapy will then
19 ultimately be used and have the clinicians understand what
20 that means to those patients so that they can explain to
21 the patients, "These are your potential risks and
22 benefits." None of the drug therapies that we've seen to
23 date have no risks. They all have some risks, and in order
24 to be able to weigh the benefits to the risks, we need to
25 be able to identify in what patient group that occurs.

1 This is a whole lot of language, and it's a
2 whole lot of language because it's taken from part of our
3 regulations, and most of our regulations tend to be
4 relatively wordy. But because of the recognition that some
5 of these things occur over a long period of time, the
6 agency expects that what we may find and what is permitted
7 within the regulations is to identify surrogate endpoints
8 which could be established in a shorter period of time.
9 Those surrogate endpoints would be the basis for the
10 approval of a new drug. The assumption would be that those
11 surrogate endpoints would ultimately be validated with some
12 more clinically obvious endpoint, but that it wouldn't
13 happen prior to approval, that the particular sponsor of
14 the application would either continue that trial or do
15 other trials to validate the surrogate endpoint, and the
16 validation of the surrogate endpoint might happen 1 year, 2
17 years, 5 years, 10 years later.

18 The drug would be approved on a surrogate, and
19 the approval would be similar to any kind of other. It
20 would be a full approval of that product, with the
21 exception if ultimately the surrogate endpoint was not
22 validated, it would be easier for the agency to remove the
23 product from the market. Under current law and
24 regulations, it is relatively difficult for the agency,
25 once a product is approved, to remove that product from the

1 market. This provides an easier mechanism to do that
2 should the surrogate not be validated, but up until that
3 point, it is essentially full approval.

4 Because of the long time frames, the agency
5 envisions this is a likely pathway that many of these
6 products may end up following, and part of the discussion
7 we'd like to have today is to see if there are endpoints
8 which people believe could be used as surrogates that would
9 later be validated, and if they can be used as surrogates,
10 what types of studies would best be done as validating the
11 surrogates or possible things that could be done to
12 validate the surrogates. As I said, this language just
13 describes that it's all permissible within the regulations.

14 In the past we have accepted a number of
15 different endpoints as being definitive clinical endpoints,
16 and I've switched from surrogates to these are things that
17 we have said in the past and, in some cases, approved
18 products or, in some cases, committed that we would
19 potentially approve products if these endpoints were met.
20 They've been established over a period of time in
21 consultation with a number of different groups and, in most
22 cases, with data supporting them in some form. And for
23 most of the ones that I'm going to present here, the
24 expected minimum length of the trial where they were
25 showing this was 1 year.

1 The first of these, as we've heard a number of
2 different times, is showing a mean difference in groups in
3 visual acuity of at least three lines. In other words,
4 it's doubling the visual angle, and in this case the three
5 lines was an ETDRS-type chart, and when I say that, it's a
6 chart that had equal spacing between lines and an equal
7 number of letters per line. The ETDRS chart is one of
8 those that meets that criteria, but the criteria that we
9 have said was we wanted equal spacing between lines and
10 equal number of letters per line. And if you showed a
11 doubling of the visual angle, we would readily accept that
12 as proof of efficacy.

13 Another way of looking at the visual acuity
14 question -- and before I go on, these in all cases have
15 been best corrected distance visual acuities, and
16 everyplace where I'm using "visual acuity," I'm implying
17 that it's best corrected distance visual acuity -- was to
18 look at the percentage of patients that had a particular
19 event, so not looking at the means, but looking at
20 individual patients and counting up whether patients met
21 the criteria or didn't meet the criteria, and we have
22 accepted greater than or equal to three lines of visual
23 loss in a particular patient, four lines and six lines.

24 You may ask, well, why do we pick different
25 numbers? These things do actually end up showing different

1 types of things. The six lines obviously is a much greater
2 loss, and control groups tend to have less of that. So
3 it's possible to have a lower percentage of patients that
4 have a six-line visual loss and still show significance,
5 whereas the three lines of visual loss, in many cases
6 control arms, including placebo arms, will show a
7 percentage of patients that have three lines of a
8 particular event. It's much more common in three lines,
9 obviously, than it is in six lines, so we get different
10 percentages, and it ends up being different criteria.

11 Because we recognize visual acuity as not the
12 only endpoint, we have also taken visual field as a
13 parameter and have readily accepted a mean difference in
14 visual field of at least 10 decibels. Ten decibels is a
15 relatively high change, it is well above what is expected
16 in a normal variation, and a mean change is recognized by
17 both everybody as being a real change in the visual
18 function of that patient.

19 We have taken, in some cases, some anatomical
20 or some things that are non-visual function. Reductions in
21 percentage of patients with vitreous hemorrhage. This goes
22 to the same type of thing. We've looked at individual
23 patients and said, "Did you have a vitreous hemorrhage or
24 did you not have a vitreous hemorrhage?," and we've taken
25 vitreous hemorrhage because it's been viewed as a

1 particularly bad event for that patient. This is not as
2 firmly established and has been more controversial than the
3 visual function endpoints, but to date it is something that
4 we have gone and accepted.

5 Another one that's in the same kind of category
6 is percentage of patients with rubeosis. The feeling that
7 the rubeosis was directly tied to the potential for a
8 closed angle and the risks for glaucoma because of it was
9 the rationale for why this criteria was accepted. Again,
10 it was not as clear-cut as the other endpoints, but it has
11 been accepted in the past as a clinically significant
12 event.

13 Retinal detachments were also felt not to be
14 good events for patients, clear, by themselves, without any
15 other complications, either because they directly lead to a
16 dramatic loss of vision or they have the potential,
17 depending on what their location is, to lead to a clear
18 loss of vision. Consequently, they in and of themselves,
19 if you were to show a statistically significant difference
20 in the percentage of patients with retinal detachments,
21 have been accepted as an endpoint. This is a pure anatomic
22 change.

23 In discussions we've had so far, although we do
24 not have any of these validated, the following were
25 potential suggestions that were just placed out for this

1 meeting of potential surrogate endpoints, and the potential
2 things that I put out in this next group are merely
3 presented for discussion and have not so far been accepted
4 by the agency either as surrogates or as final endpoints,
5 but could potentially be either if the agency ultimately
6 decides to use them. For that reason, I'm presenting them
7 and would be interested in any discussion by the committee
8 on how relevant these are as surrogate endpoints, and if
9 they are to be used as surrogate endpoints, what it would
10 take to go and validate them.

11 One of the proposals has been a mean eye
12 difference in the ETDRS retinopathy scale of at least three
13 steps. This is contrary to what you've heard before, where
14 it would be two steps, but this would be a three-step
15 change, and it was listed as a three-step change because it
16 was considered to be well beyond what the interobserver
17 variation was. As you saw, some of the rates for
18 individual investigators running somewhere in the 80 to 90
19 percent rate for correlation of a two-step, this would put
20 it well -- not well, but would put it above that rate.

21 Switching back, this is a change in the
22 percentage of patients with a particular event, and this
23 would be counting patients with at least three steps of
24 sustained change or at least six steps of change. This
25 goes back to the issue of -- and it's put in here to raise

1 the question, do we want things that are over a course of
2 time? And if we say sustained change, then we need to
3 define what period of time we're talking about. Is this
4 the same event that has occurred over the course of 3
5 months, over the course of 6 months, over the course of 1
6 year? These would be what would be asked to be
7 established.

8 As has been addressed a little bit, one of the
9 things that we've been considering has been a mean change
10 in macular thickening. There are a number of instruments
11 that are currently being developed, and they have not been
12 established at this point as being clear, definitive
13 clinical endpoints. Because they are relatively new, it's
14 another one we would suggest potentially could be a
15 surrogate endpoint that would ultimately be validated by
16 some measure later on.

17 Resolution of fluorescein leakage has been
18 discussed a number of different times, not necessarily for
19 diabetic retinopathy, but in the case of cystoid macular
20 edema. Cystoid macular edema and diabetic macular edema
21 are not the same entities, but they share some of the same
22 features, in that they are frequently evaluated with the
23 use of fluorescein. Proposals for cystoid macular edema
24 have been that it would be an acceptable endpoint if you
25 cleared the fluorescein leakage. To date that has not been

1 accepted as a clinical endpoint. It has been suggested as
2 a possible endpoint if it could be validated with some type
3 of visual function testing. That has not happened at the
4 present time. I bring it up because of the differences
5 between cystoid macular edema and diabetic macular edema.
6 It may be a possibility within diabetic macular edema.

7 And as I started this particular group, these
8 are not firm proposals. These are suggestions as starting
9 points for the committee, and we'd be very interested in
10 opinions both on these and potential others, but do not
11 feel bound by this last group.

12 We would like at some point, as the discussion
13 goes on, to talk about what are appropriate control arms.
14 The agency has clearly accepted placebo-control arms for
15 most things as being the cleanest. That is not always
16 possible. It is not always the cleanest. But it is one
17 possibility that may be considered.

18 Dose ranging is also particularly helpful.
19 Because these trials are likely to be long-term trials, we
20 may not get the opportunity to do short, what would be
21 Phase II trials in dose ranging, trying to select the best
22 dose and then have that dose go on to a Phase III trial.
23 It may be necessary to, in the trials that are done,
24 because of the length of time, start off with multiple
25 doses and just end up with basically skipping what is

1 typically a Phase II step. If we skip a typical Phase II
2 step, that means that we probably should be putting some
3 dose ranging arms in the final trials. Again, I'd be
4 interested in particular comments.

5 Other potential possibilities are to do direct
6 comparisons against either PRP or photocoagulation. These
7 are not straightforward, for reasons that I know a number
8 of you can imagine, but we would be interested in comments
9 about whether you think that's something that should be
10 pursued.

11 The questions that the agency has posed for the
12 committee -- and I'll go through them just very briefly,
13 because I think we'll come back to them directly after some
14 open discussion -- include, is each of the clinical
15 endpoints that we have considered in the past as clear
16 clinical benefit considered by this group still to be clear
17 benefit, or should we consider removing some of the things
18 that we've currently placed on that list?

19 Are there additional things that are not
20 currently on the list that should be considered in and of
21 themselves clear clinical endpoints that would not need to
22 be validated in the future, and if you do believe that they
23 are clear endpoints, what data currently exists to support
24 that as a clear benefit?

25 Is each of the proposed surrogate endpoints

1 considered to be a recognizable surrogate endpoint? As I
2 mentioned as I was going through these, these were placed
3 up there just to give the committee a starting point. And
4 are there additional proposed surrogate endpoints? Again,
5 if we choose surrogate endpoints, then we need to try and
6 establish what would be the ultimate validation for that
7 surrogate endpoint, meaning what type of trial designs,
8 what the duration should be, and what the expected ultimate
9 outcome for the validation would be.

10 The earlier slide asked for what the best would
11 be. Recognizing that the best is not the only option, we
12 would also look at other things, but sometimes it's helpful
13 in giving guidance to people to select what you think is
14 the best in addition to selecting what others are.

15 And then, of course, the catchall to put
16 anything else that I haven't already covered, if there are
17 other issues that we should be considering that I haven't
18 mentioned on there, the agency is clearly interested in
19 knowing about them.

20 I want to thank you very much, and I'll take
21 any questions.

22 DR. BONE: Thank you, Dr. Chambers.

23 Perhaps we'll just go around, as we did after
24 the first group of speakers, and ask for questions related
25 to specific aspects of Dr. Chambers' presentation, and I

1 think really the discussion points we'll get into later.
2 This is mainly for the clarification of issues or adding
3 information.

4 Perhaps we'll start with Dr. Freeman.

5 DR. FREEMAN: I think that Wiley raised a very
6 important point, and I think it's a point that has
7 clarified for me the confusion between the ophthalmologists
8 and the endocrinologists and internists, and that is, we
9 now have a pretty good treatment for diabetic macular edema
10 and for proliferative diabetic retinopathy, and in
11 conversations during the break, it's very clear that many
12 people don't understand why we can't still use vision. I
13 think what Wiley has raised is important, and that is, if
14 we are going to use visual acuity or a standard measure of
15 vision as an outcome, we would have to really pit the drug
16 against laser therapy, and maybe that's really what needs
17 to be done, because you have a treatment whose effect is
18 very clear, there are side effects of this treatment, and
19 if I were a patient, I'm not so sure that I would say,
20 "Yes, give me 20 years of taking a tablet once or twice a
21 day, with whatever side effects, versus doing a PRP to
22 treat proliferative diabetic retinopathy," or maybe I would
23 want my macula lasered as opposed to requiring long-term
24 therapy.

25 So I think really the issue is whether this

1 drug -- and the assumption is that the drug would be better
2 -- if we could prevent retinopathy or prevent it from
3 getting worse, it would be better than a laser treatment.
4 But I don't know that, and I'm not sure we know that, and I
5 think Wiley raised that point, and that's a very important
6 one.

7 DR. BONE: Dr. Carney, questions concerning Dr.
8 Chambers' presentation?

9 DR. CARNEY: I noticed in some of the outlined
10 clinical benefits that he had down, some of them actually,
11 I think, probably related to some of the previous studies,
12 and I think as far as endpoints are concerned with regard
13 to clinical evaluations -- and that's what you'd want to
14 kind of point these things to so that they are feasible for
15 clinicians to use in the future with regard to treatment of
16 diabetics -- changes in visual loss with regard to lines is
17 very good.

18 I'm not sure I understood when you had in the
19 clinical benefits endpoint the mean difference in the
20 visual field. That was basically used as a treatment
21 design in the DRS. Was there going to be a treatment
22 effect of the drug that you're understanding is going to
23 change the visual field?

24 DR. CHAMBERS: Correct. The assumption would
25 be that there would be a difference between the groups,

1 either the drug group versus the control group, that showed
2 the drug group having better visual fields by at least a
3 mean difference of 10 decibels.

4 DR. CARNEY: Okay. And, again, in designing
5 trials where clinicians would be able to use your results,
6 how easy is it going to be to assess retinal thickening by
7 machines? Are they going to be readily available and not
8 cost prohibitive in the offices for other people? And I
9 think that the resolution of fluorescein leakage is
10 probably not one that would be considered very good for
11 diabetics as a surrogate endpoint.

12 DR. CHAMBERS: Each of those were listed as
13 potential surrogates, and they do have potential problems,
14 for exactly some of the reasons that you're talking about.
15 Absolutely.

16 DR. BONE: Dr. Davidson, any questions for Dr.
17 Chambers?

18 DR. DAVIDSON: Not being an ophthalmologist,
19 again, I would like to ask the question, an endpoint for --
20 any visual deficit must be an endpoint. Why cannot we use
21 that as an endpoint?

22 DR. CHAMBERS: Well, they've clearly been
23 proposed. I mean, those are possible endpoints. The
24 question is whether there are other things, and the answer
25 may be no. There's no question about that. But it may not

1 be the only answer, and that's part of why we're having
2 this discussion.

3 DR. BONE: Dr. Mindel?

4 DR. MINDEL: Two questions. One of your slides
5 said that one-third of macular edema spontaneously
6 resolved. I think I'd like you to point out or agree with
7 me or disagree with me that macular edema is not the same
8 as visual loss.

9 DR. CHAMBERS: Oh, absolutely agreed.

10 DR. MINDEL: Okay. So what you're saying is
11 that a third of patients, let's say they all had 20/20,
12 they could still maintain 20/20 vision, and the macular
13 edema could come and go. Some of those would have
14 significant loss, but there's a difference between macular
15 edema and vision loss.

16 DR. CHAMBERS: Correct.

17 DR. MINDEL: Now, do you have any idea what
18 percentage of patients that have macular edema and vision
19 loss spontaneously resolved?

20 DR. CHAMBERS: I do not know the answer off the
21 top of my head, and I'm not sure, but some of the people
22 who did some of those trials may actually be in the
23 audience. But I don't know if they know the answer.

24 DR. BONE: Dr. Ferris is approaching the
25 microphone.

1 DR. CHAMBERS: I actually think there were two
2 trials that did that, but Dr. Ferris was involved in at
3 least one of them.

4 DR. FERRIS: Well, in the early treatment
5 diabetic retinopathy study, we looked at improvement in
6 visual acuity after visual loss. If you have 20/20 vision,
7 it's hard to improve, so we took those who had 20/40 or
8 worse and looked for a three-line improvement, a halving of
9 the visual angle, going from 20/40 to 20/20 or 20/100 to
10 20/50 or better, and looking at that, approximately 17
11 percent of treated eyes improved after treatment.
12 Spontaneous improvement to that degree was lower.

13 DR. MINDEL: Do you have a handle on that?

14 DR. FERRIS: What, lower spontaneous
15 improvement?

16 DR. MINDEL: Yes.

17 DR. FERRIS: It was around 10 percent of those
18 that had clinically significant macular edema. Less than
19 10 percent. I don't know the exact number off the top of
20 my head.

21 DR. BONE: Could I just interject a quick
22 question? How did that relate to the repeatability of the
23 measurement?

24 DR. FERRIS: Well, that's the problem with
25 macular edema. Anybody who takes care of patients knows

1 that their vision and visual acuity can be very variable.
2 In fact, they can be variable during the day. It may be
3 worse in the morning and typically get better in the
4 afternoon, after they've been up and doing things. A
5 three-line change is a fairly extreme change in that kind
6 of variability, but that's why we see something like maybe
7 10 percent of those with macular edema having that degree
8 of change at any one visit.

9 But there's sort of a regression-to-the-mean
10 phenomenon here. If you measure it at the worst and then
11 you measure it at the best, you find these differences.
12 Unlike you and me, whose visual acuity tends to stay quite
13 stable, if you have fluctuating vision and then you add on
14 top of that error in measurement, you find a certain
15 percentage of these three-line changes or better.

16 DR. MINDEL: So I think it's fair to say that
17 using visual acuity as an endpoint has some problems.

18 DR. CHAMBERS: I would agree with that.

19 DR. MINDEL: Now the second question. One of
20 your slides, I don't think you meant what you said on the
21 slide and said. You said that you need an endpoint for
22 study that you need to apply clinically, and I don't think
23 you really meant that. I think you meant an entry point
24 that you can apply. In other words, if I have a \$50
25 million machine that will guarantee reproducible results

1 from a drug and I show convincingly, using that, that it
2 works, the clinician doesn't have to buy a \$50 million
3 machine to show it. That's the purpose of drug studies.
4 We do bioavailability, all kinds of funny things that the
5 clinician doesn't have to do. So what you need, if
6 anything, is a similar entry point, not a similar endpoint
7 for using the drug.

8 DR. CHAMBERS: What we need to be able to do is
9 translate the findings of the studies into a label, whether
10 that be what the outcome is or whether that be what the
11 entry criteria are. But we need to be able to translate
12 what we found into a drug label, and that's the extent of
13 it.

14 DR. MINDEL: Right, but I still think that what
15 you're saying is an entry point, that this drug is
16 indicated for the treatment or the use of such and such,
17 and you're not saying that --

18 DR. CHAMBERS: I am not saying that you need to
19 have that -- that everybody needs to buy that particular
20 instrument to be able to use this drug. Yes, I am not
21 saying that.

22 DR. BONE: Do I understand this, sort of
23 speaking as an old drug developer, that what we're really
24 talking about is the same indications should be
25 recognizable in the trial and in the clinic?

1 DR. MINDEL: That's what we're talking about,
2 yes. That's right. It's a starting point, and the
3 starting point may just be the diagnosis of diabetes that
4 will start the drug for the edema and the complications
5 right from the time the diagnosis is made. But you have to
6 have some criteria for entry.

7 DR. BONE: Dr. Cara?

8 DR. CARA: No questions.

9 DR. BONE: Dr. Wilson?

10 DR. ROY WILSON: I have two.

11 DR. BONE: This is Dr. Roy Wilson speaking.

12 DR. ROY WILSON: I have two questions. The
13 first is, one of the differences between what the agency
14 considers a potentially acceptable surrogate endpoint and
15 what was presented by the presenters is a three-step change
16 versus a two-step change, and one of the weaknesses in the
17 two-step change was the amount of agreement. Do you have
18 any data in terms of how much that agreement increases with
19 a three-step, or is that something that somebody has?

20 DR. CHAMBERS: I don't have it in front of me.
21 As I recall, when I've looked at it, it's in the very high
22 90s, somewhere between 95 and 99 percent.

23 DR. ROY WILSON: Okay. The second question I
24 have is really very similar to what Dr. Mindel was getting
25 at, and that deals with the resolution of macular edema.

1 What stage of macular edema were these resolutions in? Was
2 it in the clinically significant macular edema with center
3 involvement and impending center involvement, which is
4 really what the presenters are talking about, or was it
5 some peripheral macular edema that may not be clinically
6 significant?

7 DR. CHAMBERS: The macular edema that I was
8 referring to is based on the publication from Ophthalmology
9 in 1997, and it's the study, I believe, that Dr. Ferris was
10 talking about earlier. I think he probably knows that
11 information better than I do off the top of my head.

12 DR. BONE: This is speaking about what severity
13 of macular edema spontaneously resolved in that substantial
14 percentage of patients.

15 DR. ROY WILSON: Right, and is it the same type
16 of macular edema that you're talking about?

17 DR. FERRIS: If you look at even center
18 involved, a third might spontaneously resolve. So even the
19 more severe types of macular edema can come and go. So a
20 treatment for macular edema would have to keep that in
21 mind. I think the point that someone made about are you
22 taking a person and condemning them to 20 years of
23 treatment may not be so. You might see resolution of the
24 edema, take them off the treatment, and see if it recurs.
25 Because you'd have to recognize that it can spontaneously

1 resolve.

2 DR. BONE: Could I ask a question about
3 progression rates here? If it's essentially a problem of
4 the persistence or non-persistence, in some cases, over
5 what interval could one observe a patient with macular
6 edema without a high risk of visual loss in order to make
7 sure this was a persistent change and not one likely to
8 spontaneously resolve?

9 DR. FERRIS: That's a very good question and a
10 very difficult clinical issue as to how long you follow a
11 patient who has the center of their macula involved before
12 you intervene, knowing that if you wait, some of them will
13 resolve, but if you wait, some of them will be irreversibly
14 damaged. So then you're balancing the risks of the benefit
15 of treatment against the harm.

16 DR. BONE: Do we have an idea of how rapidly
17 the ones resolve that are going to resolve?

18 DR. FERRIS: No. In fact, if you took resolve
19 meaning ever resolve, maybe all macular edema eventually
20 resolves. It just resolves with blindness as the outcome.

21 DR. BONE: I'm talking about the ones that
22 disappear, like we were hearing about earlier.

23 DR. FERRIS: Typically, at least when I see
24 patients with diabetic macular edema, I don't view this as
25 the same emergency that I would view high-risk

1 proliferative retinopathy, where I think they need
2 treatment today. I think the patients with diabetic
3 macular edema can be followed. Often we bring them back in
4 6 weeks, 3 months, looking to see if things are going to
5 resolve and perhaps telling them if they notice any
6 worsening, to come in sooner.

7 DR. BONE: But you're telling me you don't have
8 hard statistics on what that rate is?

9 DR. FERRIS: If I could tell who resolved and
10 who didn't resolve, treatment would be a lot easier.

11 DR. BONE: Thank you.

12 DR. DAVIS: Dr. Bone, could I add a comment?

13 DR. BONE: Please. This is Dr. Davis.

14 DR. DAVIS: Dr. Ferris was sort of talking
15 about the real natural history of macular edema, but the
16 paper that Dr. Chambers referred to in his remarks and also
17 an ETDRS paper, there's another problem. The other problem
18 is when resolution is defined as, if you will, a one-step
19 change. When eyes are classified, for instance, as having
20 center involvement or not, yes or no, with no space in
21 between, there's a misclassification rate, I would say, of
22 probably 20 or 25 percent that -- it's sort of the
23 regression-to-the-mean problem. If you select people for
24 entry into an analysis even that have the center involved
25 and then look at them again, there's going to be a

1 misclassification problem.

2 I think the 33 percent that Dr. Chambers cited
3 and this paper that he cited cites the ETDRS, in the ETDRS
4 it was center involvement, not macular edema itself, but I
5 think it's the problem of no space, and that if we have a
6 distance -- if we enter eyes, for instance, for center
7 involvement that have macular edema some distance from the
8 center, and if the outcome then is the center involved, so
9 that there's obvious progression involved, we won't have
10 that misclassification problem of 25 or 30 percent.

11 DR. BONE: Thank you for that clarification.

12 I think Dr. Cara has discovered a question, and
13 then we'll go on to Dr. Seddon.

14 DR. CARA: Just as a follow-up to Dr. Wilson's
15 question regarding the two-step versus three-step change,
16 maybe you can tell me, do you know if there's a clinical
17 correlate or a clinical significance or a difference in
18 clinical significance between a two-step and a three-step
19 change?

20 DR. CHAMBERS: Well, remember, as I mentioned
21 earlier, the steps are not linear, and it depends on where
22 you are on them.

23 DR. CARA: But if you were to take a large
24 group of people with a two-step change, a large group of
25 people with what you would consider a three-step change, is

1 there going to be a difference in the incidence of
2 clinically significant visual impairment?

3 DR. CHAMBERS: I don't know that that's ever
4 been established.

5 DR. FERRIS: Well, Wiley, as you have pointed
6 out, as you go from each step on your scale, your risk of
7 developing high-risk proliferative retinopathy or your risk
8 of developing severe vision loss increases incrementally.
9 The increments are not exactly equal, and so it's a
10 classification scale, not a linear scale. But with each
11 step of progression, your risk has gone up. The reason
12 that people have used the three-step person scale or the
13 two-step eye scale is because this was thought to be a
14 clinically important worsening.

15 Now, I think you have to be very careful, in my
16 opinion, about saying we need a three-step eye scale change
17 if you're going to start with people with severe non-
18 proliferative retinopathy and look for the prevention of
19 proliferative retinopathy, because a three-step eye change
20 now basically means they're getting to high-risk
21 proliferative retinopathy, and photocoagulation before that
22 is going to be a likely confounder. So although you might
23 like that three-step change, it may be difficult to
24 actually observe it, because intervention is likely to
25 occur beforehand.

1 DR. BONE: Dr. Seddon?

2 DR. SEDDON: Just a matter of clarification.
3 You mentioned that the clinical signs and symptoms may not
4 be constant over time, and early adverse or beneficial
5 effects may be reversed later on. I assume that that was a
6 point to the fact that a randomized clinical trial design
7 would accommodate those factors by nature of the
8 randomization and also by the length of the randomized
9 trial.

10 DR. CHAMBERS: Correct, and the point was that
11 we may need to take into account a duration factor in
12 saying these things really are sustained. The question is
13 whether we use single observations or do we do things as
14 being sustained and you see them more than once to say that
15 they are clinically significant.

16 DR. SEDDON: And then, secondly, similar to
17 what Dr. Mindel mentioned, when you mentioned mean change
18 in macular thickening could possibly be based on automated
19 measurement of retinal thickness and how that would relate
20 to your previous statement about labeling of drug products
21 permitting a clinician to identify patients in whom benefit
22 is expected, I would assume, then, you meant that such
23 measurements would not be included in eligibility criteria
24 for a study.

25 DR. CHAMBERS: That's correct.

1 DR. SEDDON: Okay.

2 DR. BONE: Dr. Sloan Wilson?

3 DR. SLOAN WILSON: Dr. Chambers, I'd like to
4 get you to comment related to your rather wordy slide on
5 the fact that your regulations or the things that you're
6 held to related to the withdrawal of various drugs if they
7 do not work and if this in itself would influence or would
8 not encourage drug companies to proceed if they knew that
9 it could be withdrawn.

10 DR. CHAMBERS: Clearly, it has potential for
11 influencing companies not to proceed if they know they are
12 committed to a particular event and that they might
13 ultimately have to go and withdraw the product if it's
14 shown not to be beneficial. The expectation is, unless you
15 are reasonably confident that it will show that, you
16 probably wouldn't enter into such a trial. But there is no
17 question that it has the potential for decreasing people
18 trying that approach, yes.

19 DR. BONE: Dr. Zawadzki?

20 DR. ZAWADZKI: My question may be a
21 reiteration, but I'm a little perplexed by the
22 contributions of error here. We've discussed the variable
23 contribution of the anatomic findings and the variable
24 contributions of interobserver error. Which is greater? I
25 mean, is there more of a change in the pathophysiology over

1 time, or is there more of a difference in the perception of
2 one ophthalmologist or one reader looking at a change? I
3 mean, which are adding --

4 DR. BONE: To whom are you directing this
5 question?

6 DR. CHAMBERS: Probably anybody that can answer
7 it, and I'm not sure that I'm the one. It probably depends
8 on the particular finding you're talking about, but I'm not
9 sure that I can -- there are some events that come and go
10 more frequently than what would be observed within
11 interobserver differences, and there are others where the
12 interobserver difference is more likely to be higher. I'm
13 not sure I have a good answer for you.

14 It looks like Dr. Davis is willing to take a
15 stab at it.

16 DR. DAVIS: Clearly, the bigger the change, the
17 less likely it's due to misclassification or to observer
18 error, so I think going back to, say, a one-step change on
19 any scale is going to have a lot of misclassification. So
20 the bigger the change, the more sure we are that it's the
21 disease and not the observer.

22 DR. BONE: I think Dr. Zawadzki's question, if
23 I can try to recapitulate it, is, when we see this
24 variability, to what extent can we contribute it to a
25 change in the biology and to what extent is it a change in

1 the observation?

2 DR. DAVIS: I think when we're talking about a
3 condition -- say, the center of the macula thickened or a
4 very small new vessel -- and we see a variability in the
5 grading over a short time, I think it's mostly
6 misclassification.

7 DR. CHAMBERS: If you remember, most of these
8 are based on retinal photographs, so it's the same
9 photograph being read by different people. So there should
10 be no difference in the -- obviously, it's not a factor of
11 the patient changing. That photograph was taken at a
12 particular point in time.

13 DR. DAVIS: And that's a very good point. The
14 variability that we don't measure would be if we were to
15 have the patient come back the next day and take another
16 photograph, if the photograph was a slightly different
17 area, a lesion that was in one photograph might not be in
18 the next one, and that would be classification error, too.
19 It wouldn't be the grader's fault. But there's a lot of
20 potential for error.

21 On the other hand, if one has a randomized
22 trial of a drug against placebo and you can show a
23 difference, even with a system that has a lot of error,
24 that doesn't weaken the conclusion. If you can show a
25 difference with a clinically important system that has a

1 lot of classification error in it, that, if anything, I
2 think, strengthens the validity of one treatment being
3 different from the other.

4 DR. BONE: Thank you.

5 Dr. Spellman?

6 DR. SPELLMAN: No questions. Just a comment.

7 I'm an individual who spends most of my life taking care of
8 diabetic retinopathy in an inner city population, and I can
9 certainly say that it would be of great benefit to me and
10 to my patients to have a drug available which would prevent
11 the need for photocoagulation and also one which would
12 remove some of these other variables. So many of these
13 patients are not well controlled, they don't come to the
14 doctor often, they're going blind because they don't get to
15 me in time for photocoagulation, and I think that this
16 would help, even though some of these nuances of the
17 classifications are bothering people here.

18 DR. BONE: Thank you.

19 Dr. Molitch?

20 DR. MOLITCH: I would like to echo Dr. Seddon's
21 comment and disagree with you that I think that the
22 randomized trial does indeed take into consideration the
23 variability and the given endpoint. Whether it's an error
24 from biological change at one time to another or the reader
25 in reading the seven-field photos, the two groups that are

1 going to be compared, you're going to take into account for
2 this, and the error rates are going to be considered in the
3 power calculations for developing the study.

4 So I think that for any kind of a study,
5 whether you measure something once or twice or three times
6 as an endpoint, that same consideration applies to both
7 groups. So you can have a single event as an endpoint, you
8 can have a second meeting at 6 months later as a sustained
9 endpoint, but both of them are going to be equally valid,
10 because you're comparing the two groups.

11 I'd like to get your response to that, please.

12 DR. CHAMBERS: I guess I come back to whether I
13 would have been willing to accept the results of the DCCT
14 trial in its first or second year as being the definitive
15 endpoint for which was better, intensive therapy or
16 traditional therapy, and one of the potential explanations
17 is that the changes were relatively small changes, yet they
18 met particular criteria, and because of what was being seen
19 and without having a length of time involved in it, they
20 could be considered definitive endpoints when maybe they
21 shouldn't have been.

22 DR. MOLITCH: I think that's a duration
23 phenomenon in change in biology, but it doesn't get around
24 the same single-versus-multiple-endpoint measurements,
25 which really is taken care of with the control groups.

1 There was a clear change that occurred, an early worsening
2 phenomenon in 10 percent of patients, and that did in fact
3 happen, and it clearly was significant.

4 DR. CHAMBERS: I'm not suggesting that we have
5 to have a duration as part of this endpoint. I am raising
6 it as a question about whether we should or should not, for
7 discussion.

8 DR. MOLITCH: I think that there was also a
9 criticism about having to rely upon these as surrogate
10 endpoints and still having to look further down the road at
11 more definitive endpoints for longer-term studies, and at
12 least it seemed to me, from my understanding of the ETDRS,
13 the DRS, and the DCCT and other studies, that in fact these
14 surrogate endpoints that are being suggested today in fact
15 have been pretty well validated as good surrogate endpoints
16 for later bad endpoints of vision change and blindness and
17 need for laser photocoagulation, and I'm not sure I
18 understand why that still has to be developed.

19 I thought that we've already done that work in
20 these past studies and that we can accept these as very
21 good, well-validated surrogate endpoints at this point in
22 time. Is that incorrect?

23 DR. CHAMBERS: Well, Dr. Ferris can correct me
24 if I'm wrong, but it's my understanding that what got
25 established was that severe proliferative diabetic

1 retinopathy was something to be avoided, and that was what
2 the goals were for. It was not all forms of proliferative
3 diabetic retinopathy, and it certainly was not the high end
4 of non-proliferative diabetic retinopathy that was
5 established as endpoints. What we're in some cases talking
6 about are changes that are less than what was seen in those
7 particular cases.

8 DR. FERRIS: I think depending on how you look
9 at this data or where you're starting from the scale, you
10 might view a three-step change differently. In the DCCT,
11 for example, where the patients started at the low end of
12 the scale and had a three-step change, no clinically
13 important thing happened to those patients. I was on that
14 data monitoring committee, and we did not feel that it was
15 important to stop this trial because there was evidence
16 that perhaps tight control over a long period of time would
17 be effective.

18 And I take Wiley's point that if you were
19 studying a new drug and you had a similar early, let's say,
20 benefit with this drug, how would you know that there
21 wouldn't be long-term harm? And I think just as there
22 turned out to be long-term benefit with tight control, you
23 would like to have at least some part of a cohort that you
24 followed a long time to some clinically important outcome
25 if you were studying a drug at the early end of the

1 spectrum.

2 The things that we were talking about today
3 were at the other end of the spectrum, where I believe a
4 three-step change is more than a surrogate for vision loss,
5 it's actually a bad event for -- it's directly a bad event
6 for the patient, because it either means that they need
7 photocoagulation or they're so close to photocoagulation
8 that it's likely to happen and/or that they're at high risk
9 for vision loss, as we've shown from the studies that we've
10 done.

11 DR. BONE: Dr. Molitch, if I could understand
12 your question a little better, are you asking whether we've
13 ever seen a disparity between the kind of information we
14 would get using these anatomical endpoints and ultimate
15 effect on vision, and, conversely, has there been a good
16 relationship between the ultimate effect on vision and
17 changes seen in these anatomical endpoints in the trials
18 that you mentioned?

19 DR. MOLITCH: I think the latter, that we in
20 fact, to my knowledge, have seen pretty good correlation
21 with this, and there's no real reason to suspect that once
22 you get the kinds of changes that are being suggested, that
23 further worsening is not going to happen, and I don't know
24 that we have to insist upon long-term large-scale studies
25 to show that indeed -- to repeat what's already been done.

1 I just have one other comment, and there have
2 been several comments about the lack of either linearity or
3 logarithmic change between the steps, almost suggesting
4 that there was some sort of random or almost -- the thought
5 process in how these steps were developed is not at all
6 clear, I think, to many of us, and I've heard Dr. Davis
7 have presentations previously on how these steps were
8 developed, and perhaps that might be useful after lunch, to
9 have some idea of how these steps came about, the numerical
10 system and the grading system, to eliminate some of the
11 sort of feeling of fuzziness that I think many of us have.

12 DR. BONE: Let's plan on that, if everybody's
13 in agreement. I think that would be useful to many of us,
14 I'm sure, to have about 5 minutes or so. Would that be
15 sufficient, Dr. Davis?

16 DR. DAVIS: Sure.

17 DR. BONE: Okay. Thank you.

18 Dr. Feman?

19 DR. FEMAN: Just one concern, and Dr. Chambers
20 mentioned it early on in his presentation. There's some
21 concern that the reduction in the rate of progression of
22 non-proliferative diabetic retinopathy may have no
23 influence on the development of proliferative diabetic
24 retinopathy, which really disagrees with what Dr. Molitch
25 had said just a few moments ago. We've always been under

1 the assumption that if you slow down the endpoints that are
2 early on in the non-proliferative stage, that you will
3 influence the development of neovascularization and
4 hemorrhage and blindness in the eye, and yet there is at
5 least one paper in the recent literature that shows that if
6 you affect the rate of progression of the non-proliferative
7 diabetic retinopathy, you may not necessarily have any
8 influence on the development of the potential blinding
9 change of proliferative diabetic retinopathy.

10 DR. BONE: What was the intervention?

11 DR. FEMAN: This is a paper by Vitale, et al.,
12 and I don't recall if this is from the DCCT -- was it from
13 the DCCT or the ETDRS trial? Do you recall?

14 DR. CHAMBERS: No, I don't think it's from
15 either one of those.

16 DR. FEMAN: It was their own data. Okay.

17 DR. BONE: But what was the intervention?

18 DR. CHAMBERS: I don't believe there was one.

19 DR. FEMAN: No, there was no intervention,
20 except tighter control, and they said that just because you
21 delayed the onset of these surrogate features, you did not
22 delay the onset of the neovascularization that could
23 potentially lead to blindness.

24 (Laughter.)

25 DR. FEMAN: Well, I understand. It's just the

1 reverse of what we seem to have been talking about, but
2 this was in the discussion papers before this meeting.

3 DR. FERRIS: There are a number of issues of
4 how patients got into that trial, what their duration was
5 before they got into the trial. I think if you look at
6 data sets like the DCCT, where it's almost an experiment of
7 what's going on in the world right now, and you look at
8 progression three-step change and did that predict
9 important events like proliferative diabetic retinopathy,
10 macular edema, it very well predicted it. In fact, the
11 relative risks of the three-step change in the development
12 of proliferative retinopathy were very similar. It was
13 very predictive of who was going to progress. And as you
14 get higher in the scale, of course, it's almost an
15 oxymoron. A three-step change is a development of
16 proliferative retinopathy, so it's clearly predictive of a
17 bad outcome.

18 DR. BONE: Thank you.

19 Any other questions from the committee members?
20 Dr. Fleming, was that a question? No. Okay.

21 I just wanted to see if I can summarize for a
22 moment, as I did after the initial set of presentations. I
23 think Dr. Chambers is saying that until now the agency has
24 really limited the criteria it would recognize for
25 registration here to functional rather than anatomic

1 criteria, with the exceptions of certain catastrophes such
2 as retinal detachment, for example, where that was an
3 anatomical but also a definite clinical event. Would that
4 be a fair summary? And that the issue now is whether to
5 use some of these anatomical features, and Dr. Chambers
6 presented some suggestions about that which involved a
7 different number of steps, but I think we're all talking
8 here about sort of what might be useful as anatomical
9 measures or non-functional measures.

10 Is that a fair summary, Dr. Chambers?

11 DR. CHAMBERS: Yes, and the question is, should
12 we be taking some of these lesser amounts? That's the
13 question we're looking for advice on, whether we should be
14 moving more in that direction than we have in the past.

15 DR. BONE: But specifically I think we're
16 talking about anatomical rather than functional measures.
17 Is that a distinction that's fair here?

18 DR. CHAMBERS: I think everybody's in agreement
19 on the visual function measures. I don't think there's a
20 whole lot of disagreement on that. It's a matter of what
21 other things potentially could be taken, and if they are,
22 are they in and of themselves sufficient, or should they be
23 taken but regarded as surrogates, which would then be
24 validated later on?

25 DR. BONE: I guess it's almost -- I don't know

1 if it's a semantic or philosophical distinction, or maybe
2 both. If we're talking about anatomical measures here of
3 the disease, whether they're really surrogates or whether
4 they're just a different way of measuring the disease, they
5 may imply something about function, but they're still
6 looking at disease. We're running into this in every
7 disorder that we look at, and I guess it all depends on
8 what you're starting point is. You might say that a
9 streptococcal -- is the important thing the resolution of
10 the streptococcal infection or the prevention of acute
11 rheumatic fever, for example?

12 I mean, there's a lot of different ways of
13 looking at this sort of hierarchy of relationship between a
14 pathophysiologic process and the outcome that we're talking
15 about, and the term "surrogate," I think, becomes confusing
16 a little bit in this context.

17 DR. CHAMBERS: Well, I'm not implying -- I
18 mean, we've clearly taken what are anatomical changes. I
19 mean, the definitions within the law have to do with a drug
20 will alter either structure or function. Altering
21 structure is perfectly permissible. The question is
22 whether it is in and of itself readily accepted as a
23 clinical benefit or whether it has not yet been established
24 as being that and needs some other support by something
25 else. And when it needs other support, then I'm calling it

1 a surrogate. If it doesn't need support, if it can stand
2 on its own, then it's a clinical endpoint in and of itself.

3 DR. BONE: Thank you very much.

4 I think I'd just like to take note of the fact
5 that Dr. Alexander Fleming is here from the Division of
6 Endocrine and Metabolism, and I wondered if he had any
7 remarks to add here this morning before we wrap up this
8 session.

9 Thank you, Dr. Chambers.

10 DR. FLEMING: Thank you, Mr. Chairman, and
11 Wiley, a very valued colleague with whom I've worked very
12 closely on a number of review issues.

13 I think this dialogue between Dr. Bone and Dr.
14 Chambers has been very instructive, because that is really
15 why the committee is here today. It is to sort out the
16 philosophical basis of how we proceed in the development
17 and ultimate evaluation of therapies for this much needed
18 treatment.

19 Now, I think Wiley and I will vary a little bit
20 in our perspectives, and it may be because I am from a
21 division where we have relied on surrogate after surrogate,
22 at least in some people's opinion. One person's surrogate
23 can be another person's meaningful clinical measurement.
24 Obviously, we have approved anti-diabetic therapies on the
25 basis of how they improved glycemic control. This was long

1 before the DCCT. We've approved lipid-lowering drugs long
2 before we had any confirmation that the cholesterol
3 hypothesis was in fact useful.

4 In many ways, I think this rather complicated
5 proposition of showing some value in treating diabetic
6 retinopathy is analogous to the much simpler situation of a
7 lipid-lowering drug, when we started a couple of decades
8 ago. At that time we didn't know that there would be a
9 linear relationship between the reduction in total
10 cholesterol levels and ultimate clinical benefit. There
11 were similarly changes in how we classified patients, the
12 various outcomes that were measured. So it has taken a
13 long time to come to where we are with the treatment of
14 lipid disorders and reducing cardiovascular events.

15 I think that we need to tread cautiously as we
16 apply the terminology of "surrogate" here, and I think
17 this, again, goes to Dr. Wilson's point, in that we could
18 deter the development of effective drugs if we are to hold
19 over the head of each drug developer the notion that their
20 drug can be easily withdrawn or at least there will be an
21 expectation of an extensive confirmatory investment in the
22 drug's benefit.

23 Now, believe me, I think we've got to
24 ultimately have the answers, but it's not going to
25 necessarily come easily or quickly. We will require trials

1 like the DCCT and the major lipid intervention studies to
2 ultimately confirm the value of different interventions in
3 treating these chronic diseases, but it again comes back to
4 this dialogue between Dr. Bone and Dr. Chambers that one
5 person's surrogate could be seen as another person's
6 meaningful clinical change.

7 In my opinion, I think that we have a body of
8 evidence, as Dr. Molitch has pointed out, that suggests
9 that there is a reasonable relationship between the
10 anatomic and the functional measures involved in this
11 particular therapeutic area. So I believe that we should
12 be careful about using what is a relatively new regulatory
13 mechanism -- and that is what we call the accelerated
14 approval mechanism -- to make conditional of the approval
15 the performance of some long-term outcome study that may
16 not ever really be able to achieve its purpose, given the
17 limited resources that are involved in drug development.

18 But I do think that we will continue to debate
19 about how we do strike the balance between encouraging drug
20 development and maintaining reasonable standards of proof.
21 That really is our challenge. Obviously, we want to get
22 Dr. Spellman the treatments that he needs in the front
23 lines. He can't wait forever on that. But we also need to
24 get him the assurance to a reasonable degree that what he's
25 using is going to have the desired effect.

1 So this has been an extremely valuable morning
2 for me. I've learned a lot, and I hope that we will move
3 forward in developing some very specific guidelines or
4 guidances, let's say, that will help drug developers and
5 ultimately the patient.

6 Thanks.

7 DR. BONE: Thank you, Dr. Fleming.

8 Any further remarks from the members of the
9 committee before we adjourn for lunch?

10 (No response.)

11 DR. BONE: I think our time has been well spent
12 this morning. It got spent a little bit differently than
13 we had originally scheduled, but I think we've had useful
14 discussions about each of these points, and that should set
15 the stage for this afternoon.

16 We will resume at 1:00 sharp for comments by
17 members of the public. Again, I would remind anyone who
18 plans to make such remarks that they must sign up with Ms.
19 Riley prior to 1:00, and we'll look forward to an
20 interesting discussion this afternoon.

21 I thank everyone for their comments and remarks
22 this morning.

23 (Whereupon, at 11:48 a.m., the meeting was
24 recessed for lunch, to reconvene at 1:00 p.m.)

25

AFTERNOON SESSION

(1:05 p.m.)

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DR. BONE: This is the afternoon session of the joint meeting of the Ophthalmic Drugs Subcommittee and the Endocrine and Metabolic Drugs Committee concerning diabetic retinopathy clinical trial endpoints. It's time now for the open public hearing session. We have two speakers, I believe, for about 5 minutes each. The first speaker is Dr. Bursell from the Joslin Diabetes Center. I'd like each of the speakers to mention any potential financial interests that might be involved or pertinent to the committee's understanding of their remarks.

Dr. Bursell, please.

DR. BURSELL: Thank you, Dr. Bone, members of the committee. My association with Eli Lilly revolves around the fact that I am making some of the clinical measurements in their Phase II trial.

DR. BONE: So you're --

DR. BURSELL: I'm not paid by Lilly.

DR. BONE: I see.

DR. BURSELL: In any capacity.

DR. BONE: All right.

DR. BURSELL: This morning a lot of the discussion centered around diabetic retinopathy, especially in the latest stages of the disease process, where the pathogenesis was well established. And in terms of

1 surrogate endpoints, we've discussed retinal thickness
2 measurements and retinal permeability measurements. Our
3 focus at the Joslin, or in my laboratory, has been
4 primarily looking at factors and potential therapeutic
5 interventions that can prevent the development of diabetic
6 retinopathy. We're looking at very early stages in
7 diabetes, and we have used a measurement of retinal blood
8 flow as a physiological assay to determine the impact of
9 some of the diabetes-associated metabolic, molecular,
10 biological, cellular abnormalities.

11 What I'd like to put on the table for
12 discussion is potentially using a retinal blood flow
13 measurement as a clinical surrogate endpoint. In our work
14 on animal studies in diabetes, we've been able to identify
15 a number of metabolic abnormalities and potential cytokines
16 that modulate retinal blood flow in diabetes. In using the
17 same methodology in clinical studies, we've shown
18 comparable retinal blood flow abnormalities in clinical
19 patients with no diabetic retinopathy as we see in short-
20 duration diabetic rats.

21 Basically, what we found also in our clinical
22 studies was that the magnitude of the retinal blood flow
23 abnormality was significantly associated with the level of
24 glycemic control, so that the worse the glycemic control or
25 the A1C level, the greater the abnormality in the retinal

1 blood flow. In preliminary clinical studies looking at a
2 specific intervention in diabetic patients with no diabetic
3 retinopathy, we were able to show that over a 4-month
4 period using a particular intervention, we could normalize
5 the abnormal retinal blood flow in these diabetic patients,
6 and that in the subsequent 4-month follow-up after
7 withdrawal of the intervention, that retinal blood flow
8 normalization was maintained.

9 The problem with -- I guess the bottom line for
10 retinal blood flow is that we're at this stage unable to
11 relate a change in retinal blood flow with the subsequent
12 development of diabetic retinopathy. We do have ongoing
13 studies following patients with no diabetic retinopathy --
14 and we're 3 years down the line now -- to see if the
15 magnitude of the retinal blood flow is in fact related to
16 an earlier development of diabetic retinopathy. This study
17 obviously is going to take a long time. We can make some
18 extrapolations based on our measurements and the results
19 from studies such as the DCCT study, where in the DCCT
20 study it was shown that in the intensive insulin therapy
21 arm, you had a 76 percent risk reduction for development of
22 diabetic retinopathy in the primary intervention cohort.

23 Based on our results, where the better the A1C,
24 the more normal the retinal blood flow, it is suggestive
25 that there may be a relationship between an improvement in

1 retinal blood flow and potentially a risk reduction in the
2 development of diabetic retinopathy. So we feel that
3 retinal blood flow would be an important surrogate endpoint
4 to consider, especially when we're looking at therapeutic
5 interventions to prevent diabetic retinopathy.

6 Thank you for your attention.

7 DR. BONE: Thank you very much, Dr. Bursell.

8 The next speaker is Dr. Lloyd Aiello from the
9 Joslin Diabetes Center. Do you have any other declarations
10 to make, sir?

11 DR. AIELLO: I am on the advisory committee,
12 non-paid by Lilly, but my primary interest these days is in
13 telemedicine and early prevention of diabetic retinopathy
14 to start with. I won't get into that discussion. I'm here
15 actually -- as Ms. Riley says, I'm the old guy who works
16 for the young guy, and that probably is the case. Those of
17 you that have been around a while realize that this all
18 started in 1967, and I just have a few comments from the
19 old guy that are more clinically oriented than they are
20 oriented toward the updated science you may be talking
21 about.

22 I think the committee, for me, was a very
23 helpful and hopeful sign, in that you're looking into the
24 endpoints of the future. I think we do need to consider a
25 way to prevent diabetic retinopathy of any severity without

1 laser photocoagulation down the line.

2 I would like to say a couple of clinical
3 points. The ETDRS rate of progression by level of diabetic
4 retinopathy is clinically useful in a clinical practice if
5 you know what they are and if you sit down to learn them,
6 and they are very helpful in predicting the rates of
7 progression in a clinical setting.

8 The second thing I would warn you about is
9 visual function testing. Visual acuity in patients with
10 diabetes changes from hour to hour and day to day. Some
11 days you cannot refract the patient to the best visual
12 acuity because the blood sugar is spinning up or spinning
13 down, and when it gets down, you're going to get one
14 refractive condition, when it's up, you're going to get
15 another refractive condition.

16 Secondly, if you rely on contrast sensitivity,
17 the first diabetic change that occurs that is noted by the
18 furriers in New York City are contrast sensitivity changes,
19 the inability for them to grade furs, even without signs of
20 objective diabetic retinopathy.

21 The other thing is color vision. Patients
22 without any laser treatment will go on gradually to color
23 vision defects in the blue-yellow, and if you've spent your
24 entire life with diabetic patients, as I have, looking at
25 their eyes for the last 30 years, you come to feel these

1 things. So these are things that are my experience and not
2 necessarily something you're going to find well documented
3 in the literature.

4 Photocoagulation. I'm very happy to have been
5 involved with the development of the PRP technique in 1967
6 and 1968, but it is kind of a lousy outcome if we can
7 prevent it. Visual field defects occur over time. As you
8 follow these patients over 10, 15, 20 years, their visual
9 fields continue to constrict. The pigment changes in
10 retina continue to get worse. There's extension of the
11 lesions, extensions of retinal atrophy, and these are very
12 important and significant changes that occur over time
13 after photocoagulation. Macular perfusion goes down over
14 time, whether or not you've treated the macula or whether
15 or not it's had macular edema.

16 So the more extensive photocoagulation you do,
17 the worse these changes occur over time, so we end up after
18 20 years or 30 years with gun barrel vision and decreased
19 macular perfusion. Now, that's a heck of a lot better than
20 we had in 1968, don't let me -- but if we can do better
21 than that, there is a reason to do better than that.

22 Next point. Fundus photographs versus an
23 experienced examiner. The fundus photograph taken with a
24 35-millimeter slide camera gets you 4,000 lines of
25 resolution in discrimination. The human eye can only do

1 about 1,000 to 1,400 lines of resolution. The data you
2 collect from the photograph is good data. You can't even
3 appreciate it all if the image is in focus and so on.

4 Second point. Twenty-five percent of NVE --
5 compared to photographs, 25 percent is missed by good,
6 experienced examiners. Flat NVE can be missed. The reason
7 it doesn't come out as a significant factor is, you're
8 following these patients carefully, so you exponentially
9 increase your ability to catch that lesion. But if you
10 sent that patient away for 2 years with a clean bill of
11 health, you would have some problems. I'm not talking
12 about the retina people on your panel, obviously.

13 The issue of surrogates. I don't find the
14 photograph grading of macular edema and PDR, as proposed
15 this morning, as being outdated. I consider it updated and
16 in date. I don't think personally that anything better
17 that you have is proven as much as this has been proven.
18 It works for me clinically, it works in studies that we do.
19 I am hopeful that we will have other technical surrogates
20 that we will be able to use, such as retinal thickness
21 analyzers and blood flow, but these have to be
22 physiologically consistent. We should look at a
23 technological advance as to whether it stands up to
24 physiological consistency as we understand it.

25 The last thing I'd like to say is that I don't

1 think that a study of laser versus drug in the context that
2 we're talking about it can work, for a lot of reasons. You
3 can't get the numbers, you're not going to get patients not
4 photocoagulated that should be photocoagulated. There's a
5 whole host of problems with that. In terms of the numbers
6 and data, I would let Rick Ferris give you numbers on why
7 that's a difficult study to do.

8 With that, though, I would like to thank this
9 committee very much on behalf of people like me and on
10 behalf of the patients that we take care of. As we have
11 heard from our colleague here from close by, we must come
12 up with alternate ways for treatment and endpoints that are
13 meaningful.

14 So thank you very much for the opportunity to
15 speak here and for all the work that you're doing.

16 DR. BONE: Thank you much for your comments,
17 Dr. Aiello. Dr. Aiello, I have a question for you, if I
18 may. Did I understand you to say that you use retinal
19 photographs in your clinical practice?

20 DR. AIELLO: I always use retinal -- I never do
21 a laser treatment, for instance, without retinal
22 photographs. Retinal photographs, to me, are what I live
23 on or hang on or die on. They're very effective for
24 medicolegal purposes, they're very effective for
25 documentation, but they also sometimes give you information

1 that you may have missed in a very busy practice as you
2 move along.

3 DR. BONE: Well, I'm going to ask another one
4 of my naive questions. How burdensome is it to do the
5 retinal photography? We've understood from other people
6 that that's not really done in many cases outside of
7 clinical trials. But is that burdensome to do in your
8 clinical practice?

9 DR. AIELLO: Well, it's not burdensome in our
10 clinic, because it's part of the way we do it. What we've
11 done is -- and perhaps the question -- I was giving you my
12 clinical opinion that photographs are necessary clinically.
13 I would hesitate to compare it with our center, because we
14 specifically design an eye clinic situation which is geared
15 after four studies, to do studies. Every room is 4 meters
16 long, every room has ETDRS charts, all the photographers
17 and technicians are certified photographers. So for us not
18 to do photographs may in fact be more difficult than to do
19 them in the long run.

20 But aside from that, I probably would not
21 practice without having photographic capabilities, even if
22 I did them myself and set up some system that dealt with
23 that.

24 DR. BONE: Thank you very much, Dr. Aiello.

25 Dr. Freeman, I believe, had a comment.

1 DR. FREEMAN: Yes. In looking through this
2 material, I was very surprised at this kind of undercurrent
3 that retinal photographs and angiograms are not used in
4 clinical practice. Indeed, I would say certainly in
5 California it's the standard of care, and I'm seeing other
6 people nodding their head. Every diabetic who has changes
7 suggestive that they may have macular edema gets a
8 fluorescein angiogram.

9 Now, it is true that you could probably squeak
10 by without it. You could look, judge retinal thickness,
11 you might do photocoagulation without it, but most people
12 do it. I find it helpful. If a patient has a lot of
13 ischemia, I will back off on the photocoagulation,
14 actually, and it helps determine edema versus ischemia. So
15 I think that certainly in the hands of a retina specialist,
16 everyone's getting photos and angiograms.

17 DR. BONE: So the idea that this would
18 necessarily be a point of discrepancy between clinical
19 trials and clinical practice is actually not such a big gap
20 at all. Maybe not a gap at all.

21 DR. FREEMAN: Not in the United States, anyway.

22 DR. BONE: Well, that's who we're trying to
23 work it out here for.

24 (Laughter.)

25 DR. BONE: Dr. Feman?

1 DR. FEMAN: Taking retinal photographs is
2 really the standard of care in most parts of the United
3 States for retina specialists. I can't imagine a retina
4 specialist in my state or in any of the adjoining states
5 that does not have a camera in his office to routinely do
6 it. Not just because of the quality of care, but also
7 because of the medicolegal issues that if there was ever a
8 problem, you would need to verify that the patient had this
9 disorder, because once you do the laser treatment or what
10 have you, the disorder no longer exists in many eyes.

11 DR. BONE: So this wouldn't be burdensome to
12 become a larger part of the routine diabetic eye care?

13 DR. FEMAN: It's a standard part of care in the
14 hands of a retina specialist.

15 DR. BONE: But even for general
16 ophthalmologists would you say it would be?

17 DR. FEMAN: I don't know if every general
18 ophthalmologist has personal, direct access to a camera in
19 their office, but certainly every community has several
20 cameras around.

21 DR. BONE: Dr. Wilson, and then Dr. Spellman.

22 DR. SLOAN WILSON: Let me make my comment as a
23 retina specialist also, and I would certainly concur with
24 these other two comments. However, we're talking about
25 from a clinical standpoint and a medicolegal standpoint the

1 way in which we practice retina with photographs and
2 angiograms. We're not talking about the way in which these
3 are done in clinical studies, where you're analyzing each
4 of them and comparing them against a standard. So I don't
5 want us to confuse that as a standard of which we're doing,
6 because I don't think any of the retina specialists here
7 are doing that.

8 DR. BONE: Again, forgive my ignorant question.
9 Are the photographs acquired in the same way, and it's just
10 a question of not grading them?

11 DR. SLOAN WILSON: Yes. I think the fact is
12 that you pick up your clinical information comparing the
13 photographs and the angiograms, a combination of the two,
14 and then they are not necessarily compared with a standard
15 in the sense that they are in a big study, if that makes
16 sense.

17 DR. BONE: I see. So the films are the same,
18 but the analysis is less formal.

19 DR. SLOAN WILSON: I would think that's
20 correct.

21 DR. BONE: Dr. Spellman, and then Dr. Chambers.

22 DR. SPELLMAN: I was just going to add to the
23 point that I find them so useful, we have a digital imaging
24 system in our office that takes color photos as well as
25 angiograms. The insurance companies have gotten to the

1 point where they don't even reimburse us for taking the
2 photographs, but the photographs are so useful that we take
3 them anyway, because it makes it so much easier to follow
4 the patients and make sure they get high-quality care.

5 DR. BONE: Thank you.

6 Dr. Chambers?

7 DR. CHAMBERS: Just for clarification, at least
8 from my perspective, in the background information that I
9 sent, the expectation was not that clinicians don't take
10 photographs and certainly not that they don't do
11 angiograms. It's the frequency with which -- they're not
12 done every visit, and they're not done in as many fields as
13 might be done in a study.

14 DR. BONE: I see.

15 DR. CHAMBERS: It's frequency and the number of
16 fields, not that they're not done.

17 DR. BONE: Thank you.

18 Dr. Mindel?

19 DR. MINDEL: Can I assume we're in the open
20 discussion?

21 DR. BONE: We've actually completed the two --
22 I think we're leading on into the open discussion, yes.

23 DR. MINDEL: All right. I want to take a
24 lonely path of saying that these photographs are wonderful
25 for clinical medicine if you want them to be, and that's

1 not the question. This is a question for a drug study.
2 You can have a technique that is absolutely impractical,
3 completely impractical for clinically deciding whether
4 you're going to do photocoagulation or for evaluating the
5 patient in other ways, but for the purpose of the study,
6 whether everybody has it in his office or doesn't have it
7 in his office or the standard of care has nothing to do
8 with it.

9 And that's true of most drug studies. Once you
10 determine the drug is useful, you have two FDA studies that
11 are by the criteria you set, the clinician doesn't have to
12 prove that the drug is working in every patient. That's
13 not the goal.

14 DR. BONE: I think we were talking about the
15 question of entry point and the definition of how that
16 would be --

17 DR. MINDEL: Well, if there is an entry point,
18 I suspect if a drug is shown to prevent the progression of
19 diabetic retinopathy, you're going to want that person on
20 that very, very, very, very, very early. How early? Maybe
21 when it's diagnosed. It depends on the side effects of the
22 medication. Does the medication cause cataracts as well as
23 preventing -- you know, there's a whole host of questions,
24 but the more benign the medicine and the more effective the
25 medicine, the earlier you're going to want to start it, I

1 think.

2 Now, I'd like to now move on to how good are
3 photographs of the macula, and I'm referring to a paper
4 that Dr. Chambers used, which is the grading of diabetic
5 retinopathy from stereoscopic color photographs, and the
6 steps in that are quite large. They go in half-disc area
7 steps -- in other words, from one grade to another, you
8 have to have a half-disc area of edema, and then it goes to
9 a full disc. So it goes zero to half, half to one, one to
10 two, and then more than two. That's the disc areas of
11 edema. That's a lot of difference, to go from just the
12 smallest difference, from zero or suspected, to a half or
13 from a half to one. That's a half-disc diameter.

14 What was the agreement between two individuals?
15 The range for assessing the area of thickness was 26
16 percent. The area of thickness, when it was less than 15
17 micrometers from the center, 21.9. Call it 22. What was
18 the maximum thickness of the retina estimated? It was 45
19 percent. The maximum thickness at the center of the
20 macula, 18 percent. Now, this is agreement between two
21 people. I think that that -- and you're talking about a
22 half-disc diameter difference, minimum. I think that's
23 very poor.

24 So I want to get away from the criteria of this
25 for evaluating the drug. It becomes very burdensome --

1 now, I'm talking just about macula. I want that clearly
2 understood. I'm just talking about evaluating the macula,
3 the jewel in the crown of our vision. We talked about all
4 the noise in the background of evaluating patients, and the
5 only way you get around noise is with a large study. So
6 that number of 4,000 or 5,000 we're going to need, I think
7 the drug companies have to accept that. We're going to
8 need large studies. If we're going to worry about all the
9 different causes of visual variation and visual loss in
10 diabetics and the unreliability of the testing, we're going
11 to have to have large studies.

12 Now, suppose we just use visual acuity and the
13 need to do laser therapy as endpoints for macular edema,
14 macular evaluation. There are hundreds of thousands of
15 patients with diabetes, and there are hundreds of thousands
16 of patients with macular edema as defined by the studies.
17 There's no problem enrolling large amounts of patients and
18 following them using those as endpoints. The clinician can
19 still go around and -- we're not saying he can't do his
20 fundus photographs and treat with laser therapy the way he
21 normally does. We're not in any way precluding that. But
22 if he does have to have a laser therapy, well, that would
23 be a definite, clear-cut endpoint that would be a failure
24 of therapy. And if there was a decrease in acuity, that
25 also would be a failure.

1 I think you can make up by volume and
2 simplicity what you might not be able to achieve if you
3 have these stereophotographs. Because while it's true that
4 we follow patients -- I follow patients with photographs.
5 I don't follow them with stereophotographs, and most
6 clinicians I don't think do. Second of all, we don't have
7 them evaluated, which is a real time-consuming -- we don't
8 have them evaluated the way this study, the diabetic
9 treatment study -- that's a very time-consuming, expensive
10 way to do it. So it's not just taking photographs and the
11 clinician looking at them, but you've got to also have an
12 evaluation center. So that's what becomes really
13 burdensome.

14 DR. BONE: Thank you.

15 Dr. Davidson, is this on the same topic?

16 DR. DAVIDSON: I need to ask him a question.
17 Is that okay?

18 DR. BONE: Okay. And then we're going to get
19 Dr. Davis' --

20 DR. DAVIDSON: Not being an ophthalmologist, in
21 the specific outcome variables, there is in number two that
22 prevention of thickening involving the center of the macula
23 is a clinically important measure of therapeutic efficacy.
24 Is that true according to your --

25 DR. MINDEL: I'll say no. All right, now, why

1 am I going to say something that foolish? And it is
2 somewhat foolish. The use of clinically significant is a
3 biased term in this study. If you look at the data in the
4 notebook, the bottom graph, the clinically significant
5 edema with center involvement, by their criteria, in 2
6 years 25 percent of patients will have loss of more than
7 two lines. So from 20/20 to 20/40. That means 75 percent
8 of patients in 2 years do not.

9 So what you're saying is -- I mean, how do you
10 define clinically significant? I mean, the reason I took
11 this foolish -- just to be the advocate of something that's
12 against the flow, you're saying that 75 percent of the
13 patients are not going to lose any vision. I mean, is it
14 clinically significant to a study or is it clinically
15 significant to a patient? What's clinically significant to
16 a patient is loss of his macular vision.

17 DR. BONE: Why don't we come back to that topic
18 in a few minutes. I think there was a very good suggestion
19 that we ask Dr. Davis to talk about the grading.

20 DR. DAVIS: I'd be glad to do that. Shall I
21 come up there?

22 DR. BONE: Whichever is the most convenient
23 arrangement for you, sir.

24 DR. DAVIS: Were you looking at this graph that
25 the committee members have in your books? I just wanted to

1 perhaps clarify one thing. The graph is showing a
2 worsening of vision by a doubling of the visual angle, and
3 as you said, there were about 30 percent. That doesn't
4 mean that the other 70 percent had no loss of vision. It
5 means they had less. Maybe none, maybe improvement, or
6 less. And if we were showing a one-line loss, which is
7 important to me if my vision goes down one line, the
8 percentage would have been a lot higher.

9 So I just wanted to clarify the converse of a
10 doubling of the visual angle is not no loss of vision.

11 DR. MINDEL: Along the same lines, the graph
12 also shows only a 50 percent benefit for photocoagulation,
13 but as I understand it, not all those people who receive
14 photocoagulation where it stopped progressing improved. So
15 in that 50 percent of successes, there are patients who
16 just don't get any better. Is that true?

17 DR. DAVIS: Yes, there are a lot that don't get
18 better. The principal value of photocoagulation is to slow
19 the progression, not to bring back vision already lost.
20 It's not like a cataract extraction, and that's why it's
21 hard, as many of you know, to be a retinal surgeon, because
22 we try to keep our patients from losing vision, we don't
23 restore vision, except with a macula-off-retinal
24 detachment, and then we restore some.

25 But I'm digressing. I'm supposed to talk about

1 this classification, and if you could put the first slide
2 on, the class -- and I'm going to talk about this slide,
3 but I'm not going to talk about its details immediately.
4 The classification started out from a small study that we
5 did in Wisconsin in the 1960s, and if you just look at the
6 first digit in the levels up there, the 3 of the 35, the 4
7 of the 43, 47, the two 5s and the 6, I already showed you
8 before lunch that the levels start out at 10 and go to 20.
9 We had a classification that went logically from 1 through
10 6, without any voids in between, and that was based on
11 clinical impression, and we wrote a couple of papers about
12 it and said that if you're more advanced, the risk of going
13 to proliferative retinopathy is greater than if you're less
14 advanced.

15 It's a little bit like a race. If we have a
16 100-yard dash and you let me start at 90 yards, I can beat
17 to the finish line the greatest runner in the world who
18 starts at zero yards. It's the same sort of thing. If
19 you're already far along in the process of a disease, your
20 odds of going to the life-threatening or sight-threatening
21 stage are a lot higher than if you're at the beginning of a
22 disease.

23 At any rate, we then refined the classification
24 on the basis of diabetic retinopathy study data, we then
25 refined it some more on the basis of ETDRS data, and we

1 ended up with what we call the "final" ETDRS scale, and the
2 thing I want to point out, the scale was designed to
3 reflect risk of progression to proliferative retinopathy.
4 So it isn't any surprise that it ends up predicting what it
5 was designed to predict, and we did it in two ways. We did
6 it first by just looking at univariate scales, we looked at
7 each of the lesions, how predictive was a given lesion all
8 by itself of progression to proliferative retinopathy, and
9 then we picked out two or three of the best lesions, and we
10 combined them by hand, playing around with it, and then we
11 did multivariate statistical analyses to see if we came up
12 with anything new that we hadn't come up with by hand. We
13 didn't.

14 But the thing I want to emphasize is that there
15 is a substantial increase in risk as you go from the lower
16 levels -- this is the rate not just of any PDR, but of
17 high-risk PDR. In 1 year it goes from 1 percent up to 46
18 percent.

19 Now, this slide also shows you one other thing.
20 One of these levels is divided up into sublevels. All of
21 these levels have alphabetic subdivisions that are grouped
22 together that have about the same risk, but there was one
23 of these levels where one of the alphabetic subdivisions
24 didn't fit very well with the other four. There are 53a,
25 b, c, and d, and then there's e, and e is a rare bird.

1 There are only 92 of them in these -- this is the eye
2 assigned to deferral in 3,711 patients. So this number of
3 eyes happens to be number of patients. There's only one
4 eye of each patient in this analysis. So there were 92
5 patients who had this very severe NPDR in their eye
6 assigned to deferral, and you'll see that their risk is
7 very large.

8 Well, we've written a subsequent ETDRS risk
9 factor paper where we've actually changed the final scale a
10 little bit, which is why "final" was in quotes. But if you
11 ignore that little discrepancy -- that's going backwards in
12 this scale -- the point I want to make is that we go from a
13 1 percent 1-year risk to almost a 50 percent 1-year risk,
14 and the scale itself is very clinically relevant, as Dr.
15 Aiello commented a little while ago. If there are specific
16 questions, I can speak further to the scale, but I think
17 I've taken enough time.

18 But, Lloyd, could I see that other slide one
19 more time? I just wanted to point out something about the
20 reproducibility. On the eye scale, although complete
21 agreement is not very good, agreement within one step is
22 pretty good. It's about 90 percent. Partly for that
23 reason, we think it's -- we won't have very much
24 misclassification if we use a two or more step change on
25 the eye scale. We would have a fair amount of

1 misclassification if we used one step, but we won't have
2 very much misclassification if we use two or more steps.

3 Along the same lines, if we use the patient
4 scale, we won't have much misclassification if we use three
5 or more steps. And the macular edema scale is similar to
6 the eye scale. If we use two or more steps on the macular
7 edema scale, we won't have much misclassification.

8 DR. BONE: Dr. Davis, now, could you just
9 clarify for me, Dr. Mindel was just discussing what seemed
10 like, to my very naive understanding, a substantially
11 greater rate of discrepancy in the creating of the macular
12 edema, and would you clarify -- obviously, you're measuring
13 different things here.

14 DR. DAVIS: Well, he was describing, I think,
15 from the ETDRS -- I'm not sure what paper you had in front
16 of you, but I'm familiar with that scale. He was referring
17 to the grading of the extent of thickening. We also grade
18 the height of thickening. It's more difficult to grade.
19 But let me say also, before I speak specifically to that,
20 these have to be stereoscopic photographs. We cannot grade
21 retinal thickening on non-stereoscopic photographs. So I
22 give up. I can't do anything with non-stereoscopic
23 photographs.

24 With stereoscopic photographs, he was talking
25 about our scale that says, is there any thickening? Yes,

1 there is, it's less than a half-disc diameter, it's more
2 than a half, but less than one, it's more than one, but
3 less than two. These are sort of convenient steps, and
4 it's the same as the other scales. There will be quite a
5 bit of disagreement between adjacent steps, because imagine
6 an eye that has about one disc area of thickening. One day
7 the grader is going to look at it and say, "That's a disc
8 area, it goes above the cutoff," and another day the grader
9 is going to look at it and say, "It's not quite a disc
10 area, it goes below the cutoff."

11 So in a scale like this, there's always going
12 to be a lot of misclassification if you just go through
13 adjacent steps. So we have really never put any faith in a
14 one-step change on any scale of this kind. You have to
15 jump a step, and if you say how much variability is there
16 between a grader who says it's less than a half-disc area
17 and another grader who says it's more than one, there's not
18 much disagreement there. So we need a space in between.

19 DR. MINDEL: You know, it's true that when
20 something is close to one disc diameter, you could have a
21 difference, but when you're talking about 18 or 20 percent
22 agreement among two observers over the whole range, you're
23 saying that they aren't always that close a call. If it
24 were that close a call for those, yes, the figures would
25 just be much better than they are. We're talking about a

1 half-disc diameter.

2 In terms of the macula diameter, what would you
3 say is the relative diameter of the macula to the relative
4 diameter of the disc?

5 DR. DAVIS: Well, the reason I always talk
6 about the center of the macula is, if you go to the
7 histologists, to the clinicians, you won't get a definition
8 of the macula. Some people call the whole posterior pole
9 the macula, some people call one disc diameter radius from
10 the center the macula, some people call one disc diameter
11 centered on the center of the macula the macula. So I
12 don't care how you define it, but you'll have to tell me.

13 DR. MINDEL: Okay. Let me ask you this, then,
14 a different way. If I took a laser and aimed it at the
15 center of the macula and destroyed one disc diameter of
16 macula, what would my acuity be, do you think?

17 DR. DAVIS: Well, it would be 20/200 or less.

18 DR. MINDEL: So you're talking about the
19 difference between 20/20 and 20/200 in terms of diameter if
20 it translates into a functional difference.

21 DR. DAVIS: Well, you asked if we destroyed the
22 retina.

23 DR. MINDEL: Yes.

24 DR. DAVIS: Thickened retina is not destroyed.
25 I mean, edematous retina, even if the whole posterior pole

1 is edematous, immediately that doesn't mean your vision is
2 necessarily 20/200. It could be 20/40.

3 DR. MINDEL: You've destroyed the functioning
4 macular retina by destroying the central one disc diameter.

5 DR. DAVIS: With a laser.

6 DR. MINDEL: Yes, but I'm just saying -- I'm
7 trying to say, what is a disc diameter is a big, important
8 entity, and a half-disc diameter is a big, important
9 entity. When the steps go from one-half to one and you're
10 having disagreement, and large numbers of disagreement --
11 we're not talking about just the person that has one disc
12 diameter of edema is very close, yes. If you had just that
13 situation, as I said before, you'd probably have an
14 agreement maybe 80 percent, 85 percent. But to drop it
15 down that additional amount, even the ones -- there are
16 disagreements between a half and one, I'm sure, where
17 there's a big spread.

18 DR. DAVIS: There are going to be adjacent
19 disagreements no matter where you are on the scale.

20 DR. BONE: Could I just ask a question, though,
21 here? Maybe this will be somewhat helpful. I guess what
22 I'm disquieted by is, it seems like the trigger of
23 concurrence about two-step changes is very good, and the
24 disagreement over one-step changes is somewhat less than I
25 would have expected, given that concurrence at two, if it's

1 only 18 percent, you'd expect it to be maybe closer to
2 50/50, I guess.

3 But what I guess I'm wondering here is, are the
4 figures that Dr. Mindel referred to really typical or
5 representative of what's seen in clinical trials when this
6 kind of comparison is made? Obviously, they're from one
7 clinical trial. Would a higher rate of concurrence be more
8 typical?

9 DR. DAVIS: I don't think so. But I think
10 we're off on a side road. What we've proposed this morning
11 was not to have change in area of macular edema be a
12 "primary" outcome variable. We suggested that involvement
13 of the center of the macula was a clinically important
14 event, because it's when the center of the macula is
15 involved that vision begins to go down.

16 DR. BONE: Now, would the reliability of that
17 assessment be greater than this other issue about the
18 extent of edema?

19 DR. DAVIS: If there is a distance, if the top
20 of the eligibility range says the thickening can be no
21 closer than so much to the center, and if the outcome,
22 then, is the center is involved, so that you in effect go a
23 couple of steps on an arbitrary scale that one could
24 define, then the reproducibility will be quite good.

25 DR. BONE: So you're telling me that to get

1 into the study, a patient would have to have an uninvolved
2 center.

3 DR. DAVIS: Yes. Not only uninvolved, but not
4 threatened at the moment. In other words, the thickening
5 would have to be, let's say, a third of a disc diameter
6 away from the center.

7 DR. BONE: Then they would have to make a
8 progression of two steps.

9 DR. DAVIS: Yes.

10 DR. BONE: Not just to threatened, but to
11 actual involvement.

12 DR. DAVIS: Yes.

13 DR. BONE: And you believe that the concurrence
14 there would be this 88 percent or so.

15 DR. DAVIS: Plus or minus 90 percent.

16 DR. BONE: Okay. And what Dr. Mindel is
17 talking about, then, is a more subtle change and one where
18 there is already involvement, it's a question of extent.

19 DR. DAVIS: Yes, and, again, I get back to the
20 one step. In a scale like this, we're not very
21 reproducible within --

22 DR. BONE: But we're talking about a different
23 thing between uninvolved and not, it sounds like.

24 Does that jibe with your understanding, Dr.
25 Mindel?

1 DR. MINDEL: No.

2 DR. BONE: It sounds to me like we're talking
3 about two different things and trying to compare the
4 percentages.

5 DR. DAVIS: I think we are talking about two
6 different things. And, actually, Dr. Mindel said himself,
7 I thought -- I thought I heard you correctly say that you
8 agree that it's clinically important when the center of the
9 macula is involved and vision starts to go down, that is in
10 itself a clinically important outcome. I thought I heard
11 you say that at one point.

12 DR. MINDEL: Yes, that's right. Sure.

13 DR. DAVIS: Pardon me?

14 DR. MINDEL: Yes, absolutely.

15 DR. DAVIS: Okay. Then, we're on the same side
16 of this argument.

17 DR. MINDEL: I'm not sure of that.

18 (Laughter.)

19 DR. BONE: Well, I think this may be a little
20 bit narrower point than we want to try to resolve here.

21 DR. MINDEL: I'd like to just -- one other
22 thing. Two things.

23 DR. BONE: Very briefly, please.

24 DR. MINDEL: Briefly. The study I'm referring
25 to is Report No. 10 of the ETDRS. It's not a study, it's

1 what they use. This is their criteria.

2 And as far as macular edema not being
3 important, I'd point out that this is the primary -- this
4 is my problem. This is the proposed primary endpoint.

5 DR. BONE: Well, I guess I'm having a little --

6 DR. MINDEL: Which is macular edema.

7 DR. BONE: Okay. Now, I think there has to be
8 some way to clarify this, even for a poor, old non-
9 ophthalmologist here, because obviously people must be
10 talking about two different things. It sounds to me like
11 Dr. Davis is saying -- he's talking about unambiguously
12 uninvolved, unthreatened center becoming involved under the
13 observation period of the trial, right? But the concern
14 that Dr. Mindel has raised is that there's not very good
15 agreement about assessment of the extent of involvement in
16 the study where observer agreement was evaluated with,
17 admittedly, the one-step differences.

18 I believe Dr. Ferris has stepped to the
19 microphone for the purpose of clarifying this for me.

20 DR. FERRIS: With regard to this particular
21 issue and the ETDRS data set, area of involvement we have
22 never used as a primary outcome variable. We've looked at
23 area of involvement as a risk factor for loss and so on,
24 and if you think about assessing area and grading the area
25 of involvement, what you see is retinal thickening, and it

1 can look like Little Round Top. I mean, it could be a
2 nice, big, clear-cut thickened area that you can get a good
3 handle on, but there can be a lot of very shallow
4 thickening, and when you're looking at a shallow thickening
5 and you think about the difference in area based on the
6 difference of where you say that thickening has receded
7 back to a normal thickened retina, that can be a very
8 difficult call.

9 So, to me, it's not very surprising that area
10 of involvement may not be as reproducible as some of the
11 other macular edema variables that we've used, and he's
12 picked one that I think is particularly hard to grade.

13 DR. BONE: So you would agree that that
14 particular measurement should not be used for this purpose.

15 DR. FERRIS: That's why we've never suggested
16 it as a --

17 DR. MINDEL: We've never suggested macular
18 thickening?

19 DR. FERRIS: Area of thickening as a primary
20 outcome.

21 DR. MINDEL: But, wait, who wrote this, then?
22 It says retinal thickening. Where did that -- this is what
23 I'm asking about. It says retinal thickening or hard
24 exudate. What does retinal thickening mean?

25 DR. FERRIS: It means that this point is

1 thickened. It's not meant to assess the extent of the
2 thickening.

3 PARTICIPANT: Speak into the microphone,
4 please.

5 DR. BONE: Okay. Let me see if I'm -- I'm
6 trying real hard to understand this. So we're trying to
7 decide, then, whether -- everybody's agreed that we cannot
8 very well assess the area of involvement, the extent of
9 involvement, but it's argued that one can pretty well tell
10 whether the center is involved or not without making a
11 judgment as to the extent. Have I said that correctly or
12 not?

13 DR. DAVIS: This is Matthew Davis again. I
14 have to go back -- there has to be an interval. If we ask
15 a grader, "Is the center involved or not?," and this is a
16 dichotomous question, there's going to be a lot of
17 disagreement because there are going to be cases that are
18 close. There's going to be thickening that's almost at the
19 center, but not quite. There's going to be very subtle
20 thickening at the center that's hard to decide is it
21 thickened or isn't it. And if we don't have a step in
22 between yes and no, if we don't have space on the scale,
23 there will be a lot of misclassification.

24 Whether it's area of thickening, whether it's
25 height of thickening in the AP dimension, or whether it's

1 the location of thickening, does it extend to the center or
2 not, these are all very similar judgments, and if there is
3 no room in between, if you allow the top of the eligibility
4 spectrum for a trial, if the top of the eligibility
5 spectrum is just a hair below the outcome, there's going to
6 be a lot of misclassification. You need to draw the top of
7 the eligibility spectrum some distance below the outcome.
8 Then there won't be much misclassification, whichever of
9 these you use.

10 DR. BONE: So Dr. Mindel is telling us that the
11 edges of these thick areas are, forgive the expression,
12 blurry, and, therefore, it's tough, and you're telling me,
13 that's right, that's why we're only going to enter patients
14 who don't have any hint of thickening anywhere near the
15 center, and then we're only going to classify the patients
16 as being affected who definitely develop thickening in the
17 center.

18 DR. DAVIS: Precisely. I hope end of
19 discussion. That's right.

20 DR. BONE: Okay. Now, there are a lot of
21 ophthalmologists and there are a lot of diabetologists
22 sitting around here. Have I sort of got this right now?
23 Did I understand the distinction? Okay. Thank you. That
24 should, I think, satisfy everybody. At least I think I'm
25 satisfied. I hope.

1 DR. MOLITCH: What about these definitions,
2 then, on page 12? These are part of this or not part of
3 this? In the middle of the page on page 12, the definition
4 1, 2, and it looks like probably 3 at the bottom. Is that
5 where we're talking about?

6 DR. BONE: I think what we're saying is, this
7 is the definition of what it means when there's definitely
8 involved center, and what they're saying is, if I
9 understand correctly, that in order to be evaluated, a
10 retina would not have involvement -- not only this
11 involvement, but the next step of involvement would be at
12 least two steps away, if I can put it that way, and then
13 would, on study, develop either the retinal thickening or
14 hard exudate within 300 microns of the center or a definite
15 plaque within 500 microns of the center as being the
16 definition of involvement of the center. Okay? Have I
17 correctly stated that? Yes or no, please.

18 DR. AIELLO: Close. Just the numbers were
19 wrong. The primary endpoint was involvement of the center,
20 and then it had to be thickening outside of 300 microns or
21 the development for imminently threatening, which is what
22 you were saying, which was where the thickening is close,
23 and these are 100 microns, or the plaque, which is close at
24 300 microns.

25 DR. BONE: Okay. This is involving or

1 threatening, and you're going to exclude the threatened
2 from this analysis?

3 DR. AIELLO: For the handouts which we handed
4 out, which were the copies of the slides from earlier which
5 were being presented here that you have, which have the
6 star on them, for macular edema there were two indications
7 that were put down, and one of them says thickening or hard
8 exudate with adjacent thickening involving the center of
9 the macula.

10 DR. BONE: So the exact center. We're not
11 talking about within a radius. We're talking exact center.

12 DR. AIELLO: That would be the endpoint. So it
13 would have had to have gone from well outside the center to
14 involve the center.

15 DR. BONE: Okay.

16 DR. AIELLO: The imminently threatening comes
17 in on the second bullet on that page, which says
18 photocoagulation when the center is imminently threatened,
19 and that's where you have these other criteria about close
20 to but not necessarily involving the center, because
21 clinicians seeing this type of progression and now the
22 imminent threatening of the macula when it was not
23 imminently threatened before would feel, rightly so,
24 compelled to treat in many of these cases.

25 DR. BONE: Okay. So now we're saying that the

1 -- we're going to call it an endpoint. One endpoint is if
2 the exact center is involved, where it wasn't even
3 threatened to begin with, or if we do photocoagulation
4 because of a threat. Okay. Very good.

5 Now, I'd like to -- we've got 3 hours left
6 here, and I think there are those who would advocate
7 finishing before that if we can, although we certainly have
8 all the time we need to discuss this. I realize that we've
9 got some very refined points that are at the center of
10 these points of discussion, but let me see if I can sort of
11 reprise the general problem here that we're trying to talk
12 about.

13 We've had a very nice description this morning
14 by Dr. Chambers as to what endpoints have been recognized
15 or are being considered, and we've had a group of eminent
16 ophthalmologists talk about some additional movement in the
17 direction of moving anatomical or -- maybe I can suggest we
18 use the term "intermediate" rather than "surrogate"
19 endpoints. It seems to me that the term "surrogate"
20 implies that what we're looking at is something that's not
21 directly the disease, and it sounds to me like we're
22 actually looking at diseased tissue and looking at its
23 extent of involvement.

24 I'm not sure I'm comfortable with the use of
25 the term "surrogate" in this sense, because retinal blood

1 flow sounds like a surrogate to me, but exudates don't
2 sound like surrogates, they sound like things that you
3 could see and potentially could touch and measure that are
4 actually the disease process itself seen. But maybe an
5 intermediate there, which is not the same thing as a
6 clinical outcome. Clinical outcome is an event, loss of
7 vision, an intervention being required, such as
8 photocoagulation. Those kinds of outcomes have been well
9 recognized. Even anatomic clinical outcomes, such as
10 retinal detachment, have been recognized.

11 The question is whether we are prepared now to
12 move to recognition of anatomical intermediate endpoints
13 which may relate to function, but are not immediate
14 measures of function. Is that a fair statement of the
15 question as far as everybody is concerned? Not the answer,
16 of course, but the question.

17 Dr. Chambers, would you say that's a fair
18 statement of the issue that we're trying to grapple with?

19 DR. CHAMBERS: Yes. I think the thing that we
20 would like to hear is, if you're proposing a particular
21 endpoint, whether it can stand on its own, and if it can
22 stand on its own, why you think it can stand on its own.
23 And if you think that it can't stand on its own, what it
24 would take to make it stand.

25 DR. BONE: Okay. I guess the question is, what

1 do we mean by "stand on its own," first of all? One of the
2 things that -- it's interesting. I've been through some
3 guidelines development in our main committee with some
4 different conditions, and one of the things that's always
5 very important for the clinicians and the researchers to
6 understand is that questions get looked at a little bit
7 differently when you're a regulatory agency. You're making
8 rules for people, and those rules have a little different
9 implication than just best scientific opinion sometimes.
10 They have sort of the force of law behind them, and they
11 have implications for how people spend hundreds of millions
12 or billions of dollars and so on.

13 So one thing that's worth all of us doing is
14 remembering the perspective that Dr. Chambers and his
15 colleagues have to bear in mind. They really have to be
16 very certain about these things or at least know what Plan
17 B is.

18 But I think what I understand is, when you say
19 "stand on its own," Dr. Chambers, do you mean how confident
20 are we of the ultimate clinical implications of the
21 anatomical intermediate change that we're looking at? Is
22 that what you're saying?

23 DR. CHAMBERS: That's correct. If you can tell
24 us why you think so, we can take it from there.

25 DR. BONE: Why that has -- what's the level of

1 confidence we can have in the clinical implications.

2 DR. CHAMBERS: Right.

3 DR. BONE: Okay. Now, it seems to me also
4 we've got a couple of other things that bear on this, one
5 of which is the degree of certainty that's necessary for an
6 individual case and an individual case in a clinical trial.
7 So it sounds like with, for example, the discussion about
8 three-step versus two-step changes, a three-step change
9 gives a very high degree of certainty even in one
10 individual, but we've been told that it depends a lot on
11 where that individual started off, whether that can
12 feasibly be achieved without the person already having
13 suffered something we wouldn't let them suffer. And then
14 the argument's been that a two-step change gives good
15 agreement, and maybe the sample size has to be a little
16 higher, but it becomes practical to do a two-step trial, to
17 do a trial where we're looking for two-step changes as an
18 endpoint, because we wouldn't lose a lot of patients to
19 intervention.

20 Have I stated that issue correctly from the
21 standpoint of everybody involved? Is there anything
22 seriously wrong with that statement?

23 Yes, Dr. Aiello?

24 DR. AIELLO: I thought the statement in general
25 was excellent, but just, again, to point out that there are

1 two types of scales we're talking about here, the person
2 scale and the eye scale, and the amount of agreement on a
3 three-step change on the person scale is very, very high,
4 greater than 87 percent, as you saw. A two-step change on
5 the eye scale also has very, very high agreement, greater
6 than the 88 percent that you saw there. So for the person
7 scale, three steps, very, very good; two steps, pretty
8 good, but maybe not what you want to have as an endpoint.
9 On the eye scale, two steps, very, very high; one step,
10 pretty good, but probably not what you want to have.

11 DR. BONE: All right. And I think Dr. Chambers
12 referred earlier to a three-step change on the eye scale,
13 or maybe that was in the handout, and there was even a
14 reference to a six-step change.

15 DR. CHAMBERS: Well, I'll give you a reference
16 of where we've been on other things, such as
17 reproducibility when measuring intraocular pressure, which
18 runs probably a couple of millimeters, yet what we take --
19 and that has good reproducibility at, say, certainly within
20 2 millimeters, and what we take generally is somewhere
21 between 5 to 7 millimeters. So we have typically had that
22 much extra threshold of certainty prior to taking
23 endpoints. I mean, as far as what we've typically accepted
24 in the past.

25 DR. BONE: Yes, although it's not completely

1 clear that that would correspond --

2 DR. CHAMBERS: I'm just stating what we've done
3 in the past. The purpose of having this committee is for
4 you to express your opinions of where you think we should
5 be going in the future.

6 DR. BONE: All right. Now, I guess what we're
7 trying to do is, for me, is there a disagreement about the
8 idea that in principle one could use anatomic intermediate
9 changes as measures of efficacy in clinical trials if they
10 were suitably validated as having adequate clinical
11 significance? Is there any disagreement about that point
12 in principle? Because that should be addressed, first of
13 all. If there's no disagreement about that, then I guess
14 the question becomes how to establish that and whether
15 certain of these already have this established for them.

16 DR. CHAMBERS: From our perspective, that's one
17 of the things we would like to hear from individual
18 committee members, to what extent they think that's --

19 DR. BONE: Okay. But looking around the room,
20 I didn't see anybody indicate that they would disagree in
21 principle with the idea that anatomic intermediate
22 endpoints would be acceptable for clinical trials if there
23 were reasonable confidence in their clinical significance.
24 Okay. Everybody's nodding in agreement with that.

25 So I guess now we're going to focus, then, for

1 really the rest of the afternoon on how we would establish
2 the clinical significance of these anatomic intermediate or
3 what formerly were called surrogate endpoints and whether
4 that level of confidence has been achieved for any of these
5 so far, and I guess a third point is how to proceed in the
6 situation that Dr. Chambers described, where initial
7 registration might be achieved based on this kind of
8 endpoint, with some reservations as to what might happen if
9 they ultimately failed to be validated clinically, and I
10 guess that implies the question, how would we go about
11 establishing that correlation in the long run if we weren't
12 already satisfied with it?

13 We have a slightly parallel situation in my own
14 field, which is the seemingly very simple field of bone
15 metabolism, by comparison, and there over the last several
16 years the FDA guidance has been, I think, informative to
17 regulatory agencies around the world, and it really
18 reflects good science, in most people's minds. There we
19 have an anatomical measurement, we can measure the density
20 of the bone in grams per centimeter of projected area. So
21 the mass or density of the bone can be measured. So that's
22 an anatomical measurement. If osteoporosis has decreased
23 bone density, then this is actually measuring the severity
24 of the disease, and we look at clinical trials for
25 osteoporosis drugs by how a test drug actually affects this

1 measure of the severity of the disease.

2 Until this morning and this afternoon, I
3 thought we were pretty sophisticated about this, but
4 obviously this is a simple thing. But there was a
5 reservation, because there have been cases in which
6 discrepancies occurred between the anatomical measurement,
7 if you will, and the clinical outcome that we're trying to
8 prevent, which is fracture. And the way this was resolved
9 was to provide for a careful preclinical evaluation of the
10 agents to make sure there wasn't any indication prior to
11 clinical trials that such a disparity was likely to occur,
12 and when we were reasonably satisfied on that point, we
13 would accept for registration a drug which had established
14 a favorable effect on bone mass or on the anatomical
15 measurement, with the proviso that an ongoing study for the
16 clinical endpoint of fracture be at least exhibiting a
17 favorable trend and be carried out to completion.

18 I don't know if something along that line is
19 sort of where we're headed with this or not, but it might
20 be, and I don't know if that would be useful experience for
21 people to reflect on.

22 Dr. Freeman?

23 DR. FREEMAN: We had discussed some of these
24 points during the lunch break, and one of the things
25 that --

1 DR. BONE: Very informally, obviously.

2 DR. FREEMAN: Very informally. One of the
3 things that seems to me of concern is that laser treatment
4 may confound this because there may be bias in who was
5 laser treated. That was explained in the morning. And it
6 seems to me that in many studies the laser treatment can be
7 standardized, and what if you build into this that if a
8 clinician feels a patient meets the criteria for laser
9 treatment either by visual acuity, which the study center
10 knows, or by the thickening of the retina, which the
11 reading center knows, that that has to be confirmed before
12 the treatment is given? Then that potential adverse
13 outcome, so to speak, would also be a very well-
14 standardized outcome, and you wouldn't have this bias that
15 certain groups are being treated earlier because the
16 clinician suspects the patient either is or is not being
17 treated.

18 DR. BONE: I see. So if I understand the
19 recommendations this morning, the recommendation this
20 morning said that you'd want to document the progression of
21 disease and only count as a primary outcome variable
22 photocoagulation in patients in whom the progression of
23 disease had been documented, and you're suggesting the
24 alternative, which would be that as part of the trial, the
25 extent of involvement or the progression of involvement

1 would be documented before laser surgery were performed.

2 All right. Well, I think those are two
3 different ways of really getting at the same thing.

4 Comments?

5 DR. MOLITCH: I was just thinking that it's
6 probably cheaper to adequately mask the ophthalmologist
7 than to require repeated photographs in these patients.

8 DR. FREEMAN: But the concern that was raised
9 by the presenter was that the ophthalmologists can't be
10 masked --

11 DR. MOLITCH: Sure they can.

12 DR. FREEMAN: Well, the ophthalmologist is
13 going to talk to the patient.

14 DR. MOLITCH: No, they shouldn't talk to the
15 patient about the treatment regimen.

16 DR. FREEMAN: But the patient may come in and
17 -- well, what was raised this morning was the patients
18 having tingling or they're having a funny taste in their
19 mouth or whatever, the clinician may know about this, and,
20 therefore, the laser, which would be a potential endpoint,
21 would be applied differently. If that wasn't the case,
22 then the randomization would take care of it.

23 In any case, there are studies where this was
24 done, where the reading center was somewhat active, so to
25 speak. I believe in the macula photocoagulation studies,

1 the degree of laser or how completed it was was actually
2 monitored real-time within a week or so by the reading
3 center.

4 None of this is a medical emergency as far as
5 the treatment, certainly not macular treatment. So that
6 might help even this thing out, because the undercurrent in
7 opinion seems to be -- or the majority of opinion -- laser
8 is an endpoint, you can't wait for patients to lose vision,
9 because you'd have to laser them first. It would be, I
10 think, fairly easy to say, "Okay, before you laser a
11 patient in this trial, the reading center has to confirm
12 that the patient meets the criteria."

13 DR. BONE: Dr. Aiello?

14 DR. AIELLO: We basically agree with exactly
15 what's been said and what was recommended, as you did say,
16 Dr. Bone, but I don't see that there is any difference
17 between the two, that photocoagulation for documented
18 disease progression would be the only one that would be
19 counted as an endpoint. If for whatever reason a patient
20 did receive laser photocoagulation but was not documented
21 for that, that would not be considered as an endpoint for
22 that.

23 So, indeed, we are looking for documented
24 progression, photographs taken prior to the laser, just as
25 Dr. Freeman is suggesting, and that is what we would

1 recommend as the endpoint. For a patient that somehow
2 received laser photocoagulation without it, since it
3 couldn't be documented and we would worry about these other
4 issues that have been brought up, that would not be
5 considered an appropriate endpoint.

6 DR. BONE: All right. Well, let me ask you
7 this question. Is there any disagreement here that either
8 of these would be regarded as a solid clinical endpoint by
9 everyone here? Either photocoagulation for adequately
10 documented reasons or photocoagulation recommended as part
11 of the study by the reading center would be regarded as a
12 hard endpoint, that's a clinical endpoint,
13 photocoagulation, and it's not really the kind of endpoint
14 that's at issue here. That's the kind of endpoint that
15 everybody would accept, I think, isn't it? Or is it?

16 Dr. Roy Wilson?

17 DR. ROY WILSON: I guess I just have a bit of
18 confusion on this topic. I agree that photocoagulation is
19 an endpoint, and I don't think there's much argument there.
20 I also agree that there is potential bias that can enter if
21 you use photocoagulation alone as the endpoint, so you need
22 something else. What I'm little confused about is whether
23 using some progression and documentation of that
24 progression as the need for photocoagulation really
25 eliminates all the potential bias, and I'm not sure that it

1 does.

2 Maybe I'm just not understanding this third
3 specific outcome, the prevention of need for laser
4 photocoagulation, because I'm not quite sure that I see how
5 that prevents bias from entering into it, and maybe
6 somebody can explain that to me.

7 DR. BONE: So you're suggesting that even in a
8 placebo-controlled trial, if the ophthalmologist has
9 somehow succeeded in unblinding the situation by the fact
10 that the placebo tastes funny or whatever it might be, that
11 there might be cases in which the same adequate degree of
12 progression to be counted might have occurred, but the
13 ophthalmologist might or might not elect to photocoagulate
14 based on his perception.

15 DR. ROY WILSON: That's correct.

16 DR. BONE: I guess to a certain extent -- Dr.
17 Ferris looks like he has a response to that. I mean, that
18 was obviously his major concern, Dr. Ferris' concern, in
19 the first place.

20 DR. FERRIS: It is my concern, and my view of
21 clinical trials after doing these for 25 years is, it's
22 impossible to totally get rid of bias. They creep in in
23 ways that you can't even predict, so you try to be
24 proactive to prevent them.

25 I think the point that you're making, as I

1 understand it, is, if you were more anxious to pull the
2 trigger, you would be more anxious to take the pictures,
3 and so there may be an unevenness in when the photos are
4 taken in that case. And because, let's say, there were two
5 identical patients, one on Treatment A and one on Treatment
6 B, and for whatever reason the doctor thought that A was
7 the active treatment, so he saw the identical thing with A,
8 but said, "Well, I'm going to give this treatment a better
9 chance" and sees it with B and goes ahead and takes
10 pictures and sends them to the reading center.

11 So I think there is some chance of bias, it's
12 just not as much as there would have been if the doctor
13 could just do it ad lib.

14 The other important thing that I think needs to
15 be built into any trial such as this is that photos are
16 taken at a regular interval so that there are consistent
17 photos on everybody at the regular intervals, so that that
18 patient that didn't get picked up at 6 months had pictures
19 taken in any event.

20 DR. ROY WILSON: Would it be mandated that if
21 you reach a certain level of progression that's documented,
22 that you have to photocoagulate?

23 DR. FERRIS: See, that's the thing that we were
24 trying to avoid, because I don't know if you've ever run
25 large clinical trials, but ophthalmologists as a group tend

1 to have their own opinions, so they may or may not agree
2 with the reading center as to whether this patient needs
3 treatment or not. It puts reading centers in an awkward
4 position, too, to be the gatekeeper on whether Mrs. Jones
5 can get treatment, whose vision is down and she believes
6 she needs treatment, the doctor believes she needs
7 treatment, the photographs weren't adequate, maybe there
8 was poor stereo, so they've got to have another set of
9 photos, and somehow the treatment is being delayed by the
10 process of the clinical trial, and then the IRBs and others
11 -- and me -- start getting concerned about whether we're
12 giving good care.

13 It's a difficult road to follow, to be giving
14 both adequate care as well as document --

15 DR. ROY WILSON: I understand that, and that's
16 why I think that bias can enter into it, because of this
17 freedom. So I guess of the three outcomes, I guess I'm
18 most uncomfortable with the third because of that, and I
19 just was wondering if I was just reading that wrong.

20 DR. BONE: Dr. Davis?

21 DR. DAVIS: Matthew Davis again. But you're
22 worried about the patient who has this progression that
23 would make them qualified for photocoagulation, that they
24 may not get it. In the endpoint we're proposing, it
25 doesn't matter whether they get it or not. That's the

1 event. The progression to the stage that allows, mandates
2 -- whatever verb you want to use -- photocoagulation,
3 that's the outcome. Now, whether the eye actually has the
4 photocoagulation or not doesn't matter. If this is a
5 patient of a very conservative ophthalmologist who doesn't
6 do it, it doesn't matter. That's the outcome.

7 The only place where the bias -- and that
8 assumes that the reading center is masked, and the reading
9 center is not -- except, as Dr. Ferris says, if it's an
10 extra visit and extra pictures get sent in, then there's
11 room for bias.

12 DR. ROY WILSON: That answered my question.
13 That's what I was looking for.

14 Can I ask another?

15 DR. BONE: I'm trying to close this issue if I
16 can, because I think this is not the controversial area,
17 and maybe what we can -- is it directly on this point?

18 DR. ROY WILSON: No.

19 DR. BONE: Well, then, we'll have lots of
20 time --

21 DR. CHAMBERS: It is a controversial area, and
22 I would like to hear from other members, too. The issue
23 is, there is not uniform agreement about when you would do
24 photocoagulation.

25 DR. BONE: Okay, that's a separate question.

1 DR. CHAMBERS: Well, you can't say that's an
2 endpoint when there's not agreement.

3 DR. BONE: All right. Can I try to take this
4 in two steps? Because otherwise I'm concerned that we will
5 get to the end of the day without having clarified the
6 questions you've asked.

7 I take it it's agreed -- and I'm kind of
8 repeating myself here -- that if a patient reaches agreed
9 criteria for photocoagulation, confirmed either before or
10 after by a masked reading center, that everybody's agreeing
11 that that's a clinical event and that that's a bad outcome
12 and that that counts as an endpoint for the clinical trial.
13 It sounds as though the questions revolve not around that
14 principle, whether that photocoagulation event is an event,
15 but about how to minimize bias, and we've had suggestions
16 of either having the documentation reviewed subsequently or
17 else before the surgery.

18 The other question has to do with what are the
19 agreed criteria for photocoagulation, and that's the one
20 that Dr. Chambers just raised.

21 So it sounds to me like we're at the point here
22 of -- let me see if I can -- I'm trying to cross off as
23 many things as we can cross off here in order to clarify
24 the points that we really need to get at, and it sounds
25 like we've gotten to the point where we can say that

1 progression to the point where there would be agreement
2 about recommendation of photocoagulation is a clinical
3 endpoint. Now I guess it's timely to discuss what would be
4 the criteria by which most people would agree on that.

5 Are we all on the same page? I'm not trying to
6 force anybody into a corner here, but I want to just make
7 sure we're going step by step. Is there good agreement
8 that that's sort of the question before us at the moment?
9 Good. Okay.

10 Now, I'd be very interested in comments on --
11 and I think Dr. Mindel wants to speak first -- on when
12 there would be concurrence amongst experts about the need
13 for photocoagulation in patients who had entered the trial
14 without central involvement.

15 DR. MINDEL: I think I can speak for my
16 department that macular photocoagulation is never done
17 without a fluorescein angiogram. Is that true sort of
18 universally? Because if it is, then that gives a well-
19 documented record that can be retrospectively analyzed, as
20 well as the stereophotographs, as to the justification.

21 I mean, criteria could be set up, for example,
22 the area of filling and involving the central macular edema
23 2 minutes after the injection, something like that.
24 Criteria could be set up involving that also. Our people
25 don't shoot the laser just at the macula, they're shooting

1 it at a leakage point or a vessel that's leaking.

2 DR. BONE: Other comments from the
3 ophthalmologists?

4 DR. FEMAN: This is Dr. Feman. Perhaps we
5 should ask Dr. Davis to comment. As I recall, the ETDRS
6 did not require fluorescein angiography to consider doing
7 photocoagulation for macular edema, and in my community it
8 is not the standard, although it's my personal standard. I
9 know many ophthalmologists in my community that will take
10 photographs, but not necessarily do a fluorescein angiogram
11 before photocoagulating for what's called clinically
12 significant macular edema.

13 DR. BONE: Dr. Seddon?

14 DR. SEDDON: I would agree with Dr. Feman. I
15 think many ophthalmologists do perform fluorescein
16 angiogram before doing macular laser treatment. However,
17 it's definitely not 100 percent across-the-board action to
18 take a fluorescein angiogram before treating, and I think
19 the studies indicate that. The diabetic retinopathy study
20 suggests that you do not need to do a fluorescein
21 angiogram. You need the stereoscopic fundus photograph to
22 assess the macular edema, but not necessarily an angiogram.

23 And my understanding is that we're talking
24 about the criteria that are established by the extensive
25 diabetic retinopathy studies in terms of when a patient

1 needs focal laser photocoagulation of the macula. My
2 understanding was those are the criteria that they will be
3 using in the study.

4 DR. BONE: Dr. Cara?

5 DR. CARA: After hearing all this discussion,
6 it sounds to me that we've kind of -- and I may be mistaken
7 here, but please correct me if I'm wrong -- that we've kind
8 of slipped more into trial design rather than really
9 considering whether photocoagulation is really an endpoint.
10 I think we agreed to that, and now I think it's the
11 responsibility of the sponsor to develop the trial design
12 that will allow appropriate evaluation of that endpoint.
13 Am I making myself clear? Whether it be done through a
14 central reading facility, whether it be done through a set
15 of agreed-upon criteria, or whatever. But I think that's
16 more of a trial design issue.

17 DR. BONE: Well, I guess Dr. Chambers' question
18 was, if I understood it correctly, is there a wide spectrum
19 of opinion about what the threshold is for photocoagulation
20 for macular edema, or is there reasonably good agreement?
21 Is this likely to be a big problem in designing trials, to
22 have well-accepted criteria for that intervention?

23 I mean, I'll ask a few of the ophthalmologists.
24 Dr. Freeman, is there a wide range of opinions about when
25 that intervention should occur?

1 DR. FREEMAN: There is a wide range of opinion
2 in practice. Indeed, at the Academy meeting a couple of
3 years ago, there was a big debate between Howard Schatz and
4 somebody else as to whether one should follow the so-called
5 ETDRS criteria and recommendations or be much looser. But
6 you could define tight criteria that I think a study
7 ophthalmologist would accept, but if you leave it to all of
8 the ophthalmologists in the study, you'll have tremendously
9 wide criteria.

10 DR. BONE: Dr. Carney?

11 DR. CARNEY: I think that's what they're trying
12 to do here, is decide are there X number of criteria that
13 we may be able to find useful in any clinical trial as
14 opposed to letting people start drug studies, decide on
15 what criteria they want to use, and then find out that the
16 study itself may not be appropriate, may not be applicable
17 to what we consider to be clinically useful vision, and
18 then have to throw it out. So if you give them some
19 baseline criteria as to what you consider will be a useful
20 clinical tool, then they can go ahead and design as many
21 drug studies as they like.

22 I think that's what they want, not to make out
23 the clinical trial itself, but to just give some useful
24 ideas on what we consider to be visually acceptable changes
25 for the study.

1 DR. BONE: So I'm understanding this discussion
2 to mean that individual clinical practice varies widely,
3 but trial design doesn't vary so much. Is that what people
4 are telling me? For the record, many ophthalmologists are
5 nodding at this. Dr. Freeman is about to speak further to
6 this.

7 DR. FREEMAN: I think we would all agree that
8 if photocoagulation is considered an endpoint, one could
9 design into a trial very clear-cut criteria that could be
10 confirmed by a reading center on vision, et cetera, et
11 cetera. But if you just let it be best medical judgment
12 photocoagulation, you have all these other potentials of
13 bias and great variation.

14 DR. BONE: Dr. Ferris looks like he wishes to
15 speak to this point.

16 DR. FERRIS: It occurred to me as I was
17 listening to this that maybe there was a piece that seemed
18 obvious, because we worked on it years ago or over a period
19 of years as we were evolving this. There are two problems.
20 One is the ophthalmologist who wants to treat too early.
21 The other one, we haven't talked about, but is an equally
22 important problem, and that is, as Bill said, there are
23 some ophthalmologists who wait until quite late to treat.
24 In fact, I was asked to write an editorial for Archives of
25 Ophthalmology about should you ever treat a 20/20 eye,

1 because there are ophthalmologists that would never treat a
2 20/20 eye.

3 So now the spectrum of when to treat is quite
4 varied, and what we were trying to do is to create some
5 rules, and the rules there that you have for the imminently
6 threatened seem to be a set of rules that we hope that all
7 ophthalmologists that would participate in a trial would be
8 willing to wait until at least that happened. And we agree
9 with Bill that we would like to have it documented in
10 writing before they do it, but we recognize there may be
11 situations where it's of an emergent nature and they feel
12 it's so obvious that they have to go ahead that day, will
13 take the pictures, and will try to retrospectively document
14 it.

15 But we also have the problem of some
16 ophthalmologists not treating when the center is involved
17 and the vision is going down, and we want to be evenhanded
18 across the trial to not just count photocoagulation, and
19 that was why we had the other center-involved criteria as a
20 bad outcome for a patient. So whether the ophthalmologist
21 chose to treat -- I mean, patients can refuse treatment,
22 too, so here's a patient with a big edema that didn't get
23 treatment. Shouldn't you count that as a failure of the
24 treatment? And whichever group they were in, we think you
25 should.

1 So that's why there are these two pieces. I
2 don't know if that helps, but that was the thinking about
3 the two sides of the issue.

4 DR. BONE: Dr. Seddon?

5 DR. SEDDON: So if the patient, then, is deemed
6 clinically eligible to receive photocoagulation based on
7 preset criteria prior to the onset of the study, whether
8 they receive photocoagulation or not is not an issue. I
9 mean, it's the fact that they've met those criteria.
10 That's the endpoint. Is that what you're saying?

11 DR. FERRIS: Well, we were going to the
12 endpoint of the center being involved. That's the endpoint
13 that I think we would all like, and then we recognized that
14 there are some patients where, because of the clinical
15 situation, the physician is not willing to wait until the
16 center is involved, nor do we think we should constrain
17 them to wait until the center is involved. So we were
18 trying to get a criteria that would get uniform agreement
19 that everybody ought to be able to wait until at least this
20 much happens. You shouldn't have to pull the trigger
21 before then.

22 We recognize that if there's this big area of
23 edema and lipid that's encroaching on the fovea,
24 particularly lipid, we're not going to be willing to wait
25 until that lipid gets into the center before we treat. We

1 can't --

2 DR. SEDDON: No, I understand. So the actual
3 treatment, then, is not part of the outcome.

4 DR. FERRIS: That's right, because we think --

5 DR. SEDDON: I perfectly agree with you there
6 are some ophthalmologists who don't like to treat eyes with
7 clinically significant macular edema if their vision is
8 20/20. But as long as we know they've reached that point,
9 then that should be considered an outcome.

10 DR. FERRIS: Right. And if we thought we could
11 get everybody to do treatment exactly the same, we'd do it.
12 We just don't -- I am sure that that's not practical in the
13 world that I live in, anyway.

14 DR. BONE: Could I just ask one -- Dr. Freeman,
15 go ahead and ask your question, and then I have one more
16 attempt to clarify.

17 DR. FREEMAN: But in other studies hasn't that
18 indeed been done, that treatment was only given when a
19 certain threshold was met and that was very carefully
20 controlled?

21 DR. FERRIS: I don't know any study that didn't
22 allow the clinician to go ahead and treat if they thought
23 that it was clinically important that day. They'll get the
24 pictures. I can't think of -- at least all the studies
25 I've been involved in, there was always that fail-safe that

1 the physician, if they thought it was clinically important,
2 was allowed to go ahead and treat the patient the way they
3 thought was clinically necessary.

4 Most of the studies do just what you said.
5 We've asked them to send the pictures ahead of time, but no
6 matter what you do, there's a day or two delay, so we've
7 always let the loophole. That's the only reason for the
8 loophole, for the patient whose vision's down, they're
9 crying in your office, "I've got to have this treatment
10 today." I'm not going to tell Mrs. Jones that, "Well, I'd
11 treat you today, except I have to send pictures to Matthew
12 Davis and get his permission to do it, even though you and
13 I both think we need to treat."

14 I think there has to be that loophole for the
15 clinically emergent situation, and we agree with you that
16 for almost all situations in macular edema, that shouldn't
17 have to be used, and we would hope that it was never used.
18 We're just leaving it there.

19 DR. BONE: Dr. Roy Wilson?

20 DR. ROY WILSON: I agree, first of all, that
21 prevention of the need for laser is better than laser for
22 the endpoint, and it seems to me that this discussion is --
23 part of it is unimportant, in that if everybody can agree
24 that the endpoint that is being offered is one that is
25 conservative enough that most people would wait until that

1 level, then it's almost a moot point as to whether or not
2 it's the exact time that most people would treat, because
3 it doesn't make a difference since the treatment is not the
4 endpoint. It's really reaching that point.

5 So, to me, whether or not this is the exact
6 point at which most people would treat or not is a
7 superfluous argument. It's really just a matter of whether
8 it's conservative enough that most people would at least
9 wait until that point, and if that can be agreed upon, then
10 it seems like we can just move on, I would think.

11 DR. BONE: Well, do you agree?

12 DR. ROY WILSON: Do I agree?

13 DR. BONE: Yes.

14 DR. ROY WILSON: I'm not a retina -- I don't
15 treat retina, so I can't speak to that. But listening to
16 my colleagues who do, it appears that they agree, and if
17 that's the case, then I don't think it's really important
18 whether treatment should be done at a later stage or not,
19 since that's really not the endpoint.

20 DR. BONE: Well, I guess the two criteria that
21 would be a clinical endpoint here are a retina that wasn't
22 threatened develops involvement of the center, actual
23 involvement, or a retina that wasn't threatened becomes
24 threatened and reaches criteria for photocoagulation.

25 Now, I'm just going to have to ask the

1 ophthalmologists here, would the criteria set up here for
2 progression from unthreatened to threatened be generally
3 accepted as reasonable in the ophthalmology community as a
4 criteria for this intervention? Maybe we can just go
5 around the table, starting with Dr. Feman.

6 DR. FEMAN: Yes, I agree.

7 DR. BONE: Okay. And Dr. Spellman?

8 DR. SPELLMAN: I agree also.

9 DR. BONE: Dr. Seddon?

10 DR. SEDDON: Yes.

11 DR. BONE: Dr. Wilson?

12 DR. ROY WILSON: I don't treat retina.

13 DR. BONE: Okay. And Dr. Mindel?

14 DR. MINDEL: I'm going to pass on that.

15 DR. BONE: You are? Okay. I'm going to come
16 back to you and ask you about that, then.

17 Dr. Freeman?

18 DR. FREEMAN: Yes.

19 DR. BONE: Okay. Now, Dr. Mindel, you want to
20 pass because it's not the area you particularly operate in
21 or because you have reservations about the question or --

22 DR. MINDEL: I think it's largely because I
23 don't practice retina full-time.

24 DR. BONE: Okay. So all the people that deal
25 with retinas have agreed that this is sort of a -- maybe

1 not exactly a consensus, but the consensus would not get up
2 and walk out of the room if this were the criteria. Is
3 that --

4 PARTICIPANT: Yes.

5 DR. BONE: Okay.

6 Dr. Chambers, does that address your concern
7 about this?

8 DR. CHAMBERS: The difficulty -- I almost hate
9 to raise it -- is not going from non-threatening to
10 threatening. It has been finding a criteria you can start
11 with that has a high enough probability of occurring that
12 through X number of steps will then achieve what everybody
13 recognizes is the time when laser should occur.

14 The argument that backs up a couple of steps
15 from that is that the risk factor now is too low and it
16 would take an inordinate number of years to ever get
17 through a couple of steps.

18 DR. BONE: So your concern is not about the
19 validity -- the concern you're describing, not your
20 personal concern. But the concern you're describing is not
21 about the validity of this progression as an indication of
22 the course of the disease, but a concern about the sponsor
23 having the resources, in effect, or the investigators
24 having the ability to recruit a large enough sample size to
25 both meet this two steps back entry criteria and get to an

1 adequate rate of endpoints?

2 DR. CHAMBERS: Because of a lot of the various
3 concerns, we have said pick an endpoint that would meet
4 criteria. There are basically three other steps. You are
5 starting three steps away from that. So that we don't get
6 into this one step or two steps. If the eye goes through
7 three different steps, randomization and bias, everything
8 else, we'll take care of that. Can you define three steps
9 before something, whatever that is, and have people go
10 through it and define that? To date, people have not been
11 able to define three steps before without getting to a
12 criteria that is so low in probability that it would take
13 years.

14 DR. BONE: Are you talking about three steps
15 per person or per eye? I'm learning this jargon now.

16 (Laughter.)

17 DR. CHAMBERS: Either one.

18 DR. BONE: So three steps per person is
19 equivalent to two steps per eye, right?

20 DR. CHAMBERS: We said pick whatever definition
21 you want to pick.

22 DR. BONE: Well, I guess the group that
23 presented this morning said two steps per eye or three
24 steps per person. That's their criteria.

25 DR. CHAMBERS: But they're talking about an 80

1 percent correlation, and we've not generally thought an 80
2 or 85 percent correlation is good enough.

3 DR. BONE: Oh, gee. Well, it's almost
4 indistinguishable from 100 percent in terms of sample size
5 requirement, isn't it? I mean, how much difference does
6 that make in sample size? A 10 percent or 15 percent
7 difference in sample size?

8 Dr. Feman?

9 DR. FEMAN: I think there's a little concern
10 that I think Dr. Chambers is stating, a concern about a
11 two- or three-step change regarding macular edema as
12 compared to a two- or three-step change regarding diabetic
13 retinopathy, of which macular edema is only one small
14 component. So your statement about a two-step eye change
15 being equal to a three-step person change is for the
16 overall gradation of retinopathy and not macular edema
17 specifically.

18 DR. BONE: Which way did I understand it? Did
19 I misunderstand that, that we're talking about this point
20 here?

21 DR. FERRIS: If you look at the two or more
22 step eye outcome variable, 88 percent agreement means
23 there's 12 percent disagreement. To get to two steps means
24 that you've agreed with them one step. So two steps is
25 beyond the agreement. So 88 percent of the time you'd

1 agree that there's only 12 percent false-positives.

2 The same is true for the patient three-step
3 change, 87 or 88 percent. There's 13 percent false-
4 positives there.

5 For the macular edema, the patients that we are
6 proposing that you would enroll, they have some edema, so
7 they're at risk for this, as opposed to just giving it to
8 all people with diabetes and hoping some develop macular
9 edema. The risk group here -- the reason that you'd be
10 willing to take a new drug is that you've got macular
11 edema. You have a 36 percent chance of losing vision.
12 Well, if you have any macular edema you're further down the
13 road to losing vision, but you have a clear-cut -- we
14 believe from the ETDRS you have a 35 percent chance of
15 having the center involved in the next several years.

16 So if you have just a small amount of macular
17 edema, that's equivalent to the two-step change, the 88
18 percent agreement there. The difference between what we're
19 saying at entry and what we're saying is the outcome
20 variable, we have data that shows that you have only a 12
21 percent false-positive rate there.

22 DR. BONE: Okay. So, Dr. Chambers, if I
23 understand Dr. Ferris correctly, he's telling us that with
24 concurrence, 88 percent agreement, they can identify a
25 group that have macular edema but are still two steps

1 removed from the clinical endpoint, and they have a high
2 risk of progression. So is that addressing your concern
3 about identifying criteria that would still allow for a
4 reasonably rich patient group at entry and still adequate
5 reliability of the measurement of the change?

6 DR. CHAMBERS: I think in most of those cases
7 there has not been adequate reliability as far as within
8 the change, and that's why we have pushed for, in general,
9 three steps. If you take a look at some of the various
10 charts as far as risks, you can go two steps apart from one
11 another and have places where the risk is not progressively
12 higher. The scale is not that well defined. We don't know
13 all the different factors to necessarily make calls at two
14 steps as being they will definitely go through those steps.
15 That's why we generally ask for a division in three steps.
16 We have not defined what those three steps have to be,
17 except that --

18 DR. BONE: Well, I guess I'm a little confused
19 here.

20 DR. CHAMBERS: The purpose of this meeting is
21 to get opinions from the people here about what they think
22 would be the best, and we'll work out what will be done
23 based on opinions that we hear. The issue is not what I
24 think. The issue is what you guys think right now.

25 DR. BONE: All right. So the people who spoke

1 this morning, if I understand -- I'm just trying to
2 summarize. I don't mean to do all the talking here, but
3 I'm trying to summarize. They're telling us that they can
4 identify a group with macular edema who have a high risk of
5 progression, who are nevertheless at least two steps away
6 from reaching the clinical endpoints that they've described
7 here, mainly central involvement or progression to threaten
8 center, which would imply photocoagulation. Have I
9 correctly stated your presentation? Okay.

10 So I guess the other question is particularly
11 for the people here, and especially for the
12 ophthalmologists, but maybe the others would like to have
13 optional comments for non-retinologists of whatever stripe.
14 Does that sound reasonable?

15 Dr. Freeman, does that sound like a fair
16 statement of a reasonable trial structure? Dr. Freeman is
17 nodding.

18 DR. FREEMAN: Yes.

19 DR. BONE: Okay. And, Dr. Carney, does it
20 sound to you like that group would be both sufficiently
21 rich in patients who would progress and sufficiently well
22 defined and adequately identified?

23 DR. CARNEY: I think so, but I just wanted to
24 ask Dr. Chambers something. Are you speaking of having
25 more definite criteria for progression? I mean, as an

1 entry criteria, patients who have involvement 550 microns
2 away from the center and watch progression of that? Just a
3 more defined stepwise progression? I'm not sure I
4 understand what the difference was there.

5 DR. CHAMBERS: What I have suggested is to
6 define sufficient criteria that people did not move through
7 two steps but they move through three steps, by whatever
8 criteria you define, so that you are clear that they were
9 moving along a scale that showed increasing severity and
10 got to a point that was agreed upon. The point that they
11 get to is generally not the most difficult. It's trying to
12 find something where you're clear that they are actually
13 progressing, and what it takes to do that.

14 DR. CARNEY: Okay. Then I find two steps and
15 the criteria they have listed here.

16 DR. BONE: Okay. Dr. Davidson, do you wish to
17 comment?

18 DR. DAVIDSON: No.

19 DR. BONE: Dr. Mindel? We can come back to you
20 if you like.

21 DR. MINDEL: Yes, come back to me.

22 DR. BONE: All right. Dr. Cara, did you want
23 to comment on this issue?

24 DR. CARA: No.

25 DR. BONE: Dr. Wilson?

1 DR. ROY WILSON: No, I'm fine with this. I do
2 have some other questions.

3 DR. BONE: We're trying to take one at a time.
4 Dr. Seddon?

5 DR. SEDDON: No, I agree.

6 DR. BONE: Okay. Dr. Sloan Wilson?

7 DR. SLOAN WILSON: I have no problems with it
8 either. I can understand where Dr. Chambers is coming
9 from, and I would think that obviously it would be nice if
10 we could always go in three steps, but I'm not certain if
11 you could answer the question of what difference in
12 timeframe the third step would add, as opposed to the two.

13 DR. BONE: Dr. Zawadzki, did you care to
14 comment?

15 DR. ZAWADZKI: No.

16 DR. BONE: Dr. Spellman?

17 DR. SPELLMAN: I agree with it.

18 DR. BONE: Speak up a little bit.

19 DR. SPELLMAN: Two steps per eye, three steps
20 per person. I agree with that.

21 DR. BONE: Okay. Dr. Molitch?

22 DR. MOLITCH: Yes.

23 DR. BONE: Dr. Feman?

24 DR. FEMAN: And I agree also.

25 DR. BONE: Okay, thank you.

1 Dr. Mindel passed.

2 DR. MINDEL: Let me voice why I have problems.
3 Looking at the same photograph of the same person when he's
4 at the same stage, you get an 88 percent agreement if you
5 allow one step. But we're talking now about progression,
6 and have we really got a handle on how good the agreement
7 is between two people evaluating photograph 1, six months
8 later evaluating photograph 2, and six months later -- you
9 know? Are we compounding inaccuracies? Because it's so
10 broad to start with.

11 DR. BONE: Let me see if I can understand. Dr.
12 Aiello, maybe you can answer this. I understood the slide
13 you just showed to illustrate that there was 88 percent
14 concurrence between two observers about two-step changes.
15 Did I understand that correctly?

16 DR. DAVIS: If I may, I'm Matthew Davis. There
17 was agreement within one step in 88 percent of cases
18 between two different evaluators evaluating the same eye at
19 two different times. As Dr. Ferris said, the converse of
20 that is that 12 percent of the time, they didn't agree. So
21 if we had an outcome that was one step higher than that,
22 maybe 12 percent of those outcomes might be
23 misclassification. The rest of those outcomes would be
24 real.

25 DR. BONE: That was only a single step.

1 DR. DAVIS: The agreement was within one step.
2 So if you go to two steps, then you're into the converse of
3 88. Now you're down to the --

4 DR. BONE: Dr. Seddon tells me that she can
5 clarify this for me, and I'm going to be eternally grateful
6 to her.

7 DR. SEDDON: I think I can. I think what
8 they're saying is the agreement was within one step or two
9 steps between two readers of the photograph at the same
10 time, not a one-step change from one time to another or a
11 two-step change from one time to another.

12 DR. BONE: I see. So 88 percent came within
13 one step of the other reader.

14 DR. SEDDON: Of each other.

15 DR. BONE: We're not talking about two steps of
16 progression.

17 DR. SEDDON: That's right. Is that correct?

18 DR. DAVIS: Yes. Thank you.

19 DR. BONE: This would mean that if --

20 DR. CHAMBERS: That's the exact same photograph
21 being read.

22 DR. SEDDON: Yes, that's correct.

23 DR. BONE: Yes, that's it. So then you could
24 calculate something about what their agreement would be on
25 a two-step change, but we haven't got that calculation. Is

1 that correct?

2 DR. DAVIS: That's correct.

3 DR. BONE: Okay. Dr. Mindel's reservation is
4 duly noted, and thank you very much for helping bring that
5 to the fore. It would be very helpful if somebody actually
6 did that calculation.

7 Dr. Molitch.

8 DR. MOLITCH: This is with respect to Dr.
9 Mindel's problem with the error and that, again, it's
10 applied to both groups, so that presumably you have helped
11 to take care of that phenomenon.

12 DR. BONE: So this might be much less of a
13 problem for a clinical trial than it would be for
14 evaluation of an individual case.

15 DR. MOLITCH: Correct.

16 DR. BONE: Where a three-step change would be
17 very helpful because of the high level of certainty that
18 that might engender in a particular individual. Is that
19 your point?

20 DR. MOLITCH: Yes.

21 DR. BONE: Okay. With fear and trepidation, I
22 ask does this mean that we've covered the macular edema
23 issues for the most part, and we can turn to the
24 proliferative retinopathy issues?

25 Dr. Wilson had a question.

1 DR. ROY WILSON: I just have a question which
2 is not macular edema or the proliferative retinopathy, but
3 both. So I think it might be good to just ask it now.

4 I just want to ask a little bit more about the
5 misclassification. Since there's really no gold standard
6 here, you may not have this data and you may not be able to
7 answer it. But I'd like to know whether you have data on
8 when there was misclassification, was there some sort of
9 adjudication or whatever to come to some knowledge as to
10 where that misclassification lay? Was it an over-calling
11 or under-calling?

12 DR. DAVIS: In some of the studies we had
13 duplicate grading, and if there was not agreement within
14 one step, a third person adjudicated the difference. Some
15 were over, some were under. If we look at going from stage
16 to stage, as Dr. Mindel said and as I mentioned this
17 morning, some of the disagreements between two different
18 visits would be that slightly different areas of the retina
19 were photographed. So there's a series of reasons for
20 misclassification.

21 DR. ROY WILSON: So the misclassification is
22 probably going to be of the non-differential type.

23 DR. DAVIS: And as Dr. Molitch pointed out, in
24 a randomized trial the misclassification is going on in
25 both arms or all three, or however many arms there are.

1 It's going on in all of the arms of the trial. So it
2 becomes an impediment to efficiency, but it doesn't bias
3 the validity of the outcome.

4 DR. FERRIS: Can I just make another comment,
5 because there are a number of ways to --

6 DR. BONE: This is Dr. Ferris.

7 DR. FERRIS: Dr. Ferris. I'm sorry.

8 There are a number of ways of dealing with this
9 12 percent misclassification rate. One of them is to
10 adjudicate and settle adjudications, and then if you
11 compare that rate, of course, it will be somewhat lower.

12 The other thing to keep in mind is that this is
13 a clinical trial with multiple assessments. So a mistake,
14 let's say, at six months, an over-call may disappear at the
15 next set of photos. So some of those problems sort out
16 too, as opposed to a patient who continues to progress and
17 maybe it was a borderline thing at six months but at one
18 year either they've been photocoagulated or it's obvious
19 that this is much worse. So some of that apparent problem
20 is helped by the fact that it's a longitudinal study, not
21 just two points in time.

22 DR. ROY WILSON: No, I understand. The point
23 of my question was I was just trying to see if there was
24 some specific pattern of the misclassification, because
25 whether there was or not, it would impact, of course, on

1 the sample size. That was the only point.

2 DR. FERRIS: Like one grader was constantly
3 over-calling or under-calling.

4 DR. ROY WILSON: That's right.

5 DR. FERRIS: In all of the studies that we've
6 done, we do that grader pair analysis, and of course you
7 find some graders that tend to over-call or under-call, and
8 then you try to go back and train them so they're not doing
9 something different than the other graders. From the
10 trialist's point of view, the closer you can get to
11 consistency in what is actually a quite difficult job, it's
12 in your favor. If you don't, then you have a lot of noise
13 and you're unlikely to find a true difference if it exists.

14 DR. BONE: Okay. Well, it's 3:00.

15 DR. CHAMBERS: You're free to go ahead and
16 leave this point for the moment, but we would like at some
17 point -- this was one proposal. The question still remains
18 if there are other things that people consider would be
19 legitimate endpoints in addition to this. But, by all
20 means, go ahead and go on.

21 DR. BONE: We haven't heard them if there are.

22 DR. CHAMBERS: I haven't heard you ask the
23 question either.

24 DR. BONE: Fine. Are there other proposals?
25 Do any members of the panel have a proposal for how to

1 construct a clinical trial or endpoints for macular edema?

2 DR. MINDEL: We have three endpoints. Is that
3 right? Visual acuity is being counted?

4 DR. BONE: Visual acuity, I think that was
5 stated to be counted for everything all the time.

6 DR. MINDEL: Okay.

7 DR. BONE: And the other two endpoints were
8 progression from not threatened to central involvement, and
9 progression from not threatened to threatened requiring
10 photocoagulation. It was proposed that this then implied a
11 two-step progression within the eye, within a single eye.

12 DR. SLOAN WILSON: Excuse me. Could I clarify
13 one thing?

14 DR. BONE: Yes.

15 DR. SLOAN WILSON: If photocoagulation were
16 done, although not necessarily recommended, that then
17 becomes an endpoint. Is that correct?

18 DR. BONE: I think that was regarded as a
19 secondary endpoint if it wasn't confirmed by the
20 photographs.

21 DR. SLOAN WILSON: Okay, secondary.

22 DR. BONE: It was photocoagulation recommended
23 or performed, confirmed by the photographs, or prior
24 adjudication as Dr. Freeman suggested. But in some way
25 independently verified, not just the ophthalmologist

1 treating.

2 Well, Dr. Chambers, it doesn't sound like
3 anybody is prepared to come up with their own today. I
4 suspect that people will think about that, and I'm sure
5 that this will be a template for other recommendations by
6 interested parties. But I guess I'm not surprised that
7 after this lengthy discussion, the members of the committee
8 didn't propose to go into business for themselves.

9 In the FDA document, the discussion of the
10 macular edema actually came in under the mean change in
11 macular thickening, and resolution of fluorescein leakage
12 under potentially acceptable surrogate endpoints. Are
13 there comments on those two suggestions that Dr. Chambers
14 mentioned? First of all, comments by members of the
15 committee. I think we'd be very interested in the retina
16 members of the committee.

17 This is on page 2 of Dr. Chambers' handout, and
18 I think these are not necessarily endpoints that Dr.
19 Chambers is advocating but endpoints that have been
20 considered. Is that correct, Dr. Chambers?

21 DR. CHAMBERS: That's correct.

22 DR. BONE: Okay. Whereas the first group were
23 ones that have been pretty well agreed upon in the past.

24 DR. CHAMBERS: Correct.

25 DR. BONE: So just to finish up the macula

1 issue, comments from members of the committee? Perhaps
2 we'll start with Dr. Freeman.

3 DR. MOLITCH: Which question are we on?

4 DR. BONE: We're trying to finish up the
5 macula.

6 DR. MOLITCH: Which question are we on?

7 DR. BONE: Well, I don't know if we're on a
8 question.

9 DR. MOLITCH: Oh, I'm sorry.

10 DR. BONE: We're looking at this handout. This
11 is the handout that was in the inside front of the white
12 book. I'm looking at page 2 of 5. It's a five-page
13 handout, and these are some other endpoints that Dr.
14 Chambers had listed as having been considered.

15 So, were there comments on the -- maybe we'll
16 just take them together. Dr. Freeman, the macula endpoints
17 mentioned in that section, do you have comments?

18 DR. FREEMAN: I would say that fluorescein
19 leakage is something that may even be an earlier process,
20 but I think it's already been decided and worked out that
21 that would probably precede the macular thickening that you
22 can see on retinal photographs. So I think we're looking
23 too early in the disease process, and I would agree with
24 not having those as endpoints.

25 DR. BONE: All right. And you would also say

1 macular thickening without the criteria that we were
2 discussing?

3 DR. FREEMAN: It's so difficult to measure, and
4 the new techniques that are available are not at all
5 standardized.

6 DR. BONE: Dr. Carney.

7 DR. CARNEY: I agree. I don't think you can
8 use resolution of fluorescein leakage. Even in good
9 control, there's leakage. Also, the thickening is too hard
10 to measure I think.

11 DR. BONE: Dr. Mindel.

12 DR. MINDEL: No comment.

13 DR. BONE: No comment, although you'd expressed
14 concern about the thickening issue earlier.

15 DR. MINDEL: I think it's been accepted.

16 DR. BONE: All right. Dr. Cara, did you want
17 to comment on this?

18 DR. CARA: No.

19 DR. BONE: Dr. Wilson?

20 DR. ROY WILSON: I agree with not including
21 this.

22 DR. BONE: Dr. Seddon.

23 DR. SEDDON: At some point, points 1 and 2 will
24 be considered?

25 DR. BONE: We're talking about that. We're

1 trying to finish up macula.

2 DR. SEDDON: Yes, but this is the section we're
3 talking about?

4 DR. BONE: Yes.

5 DR. SEDDON: So we had agreed to a two-step
6 change in the macular edema, and for number 2 you could
7 look at these other step changes, but I don't think it's
8 necessary to say it's a primary endpoint. But I think
9 those are interesting items to look at eventually in the
10 study. Numbers 3 and 4, I agree with previous committee
11 members on those two issues, that they are probably not
12 good surrogate measures.

13 DR. BONE: Thank you.

14 Dr. Sloan Wilson.

15 DR. SLOAN WILSON: If I'm correct now, let me
16 sort of summarize in my own mind here. The two-step
17 change, of course, we're talking about will be clinically
18 recognizable and a way in which the drug companies can
19 theoretically have an acceptable population, whereas
20 opposing the higher numbers, the three-step, even the six-
21 step would obviously put them far enough away so that it
22 would take a much larger group and a much longer time to
23 carry this out, but would probably be a more definitive
24 change from the FDA's standpoint.

25 Regarding the resolution of the fluorescein

1 leakage and numbers 3 and 4, the mean change, I don't see
2 that that in itself would add anything to what the clinical
3 trials could do, because I don't think we're going to try
4 to reinvent the wheel here today.

5 DR. BONE: Thank you.

6 Dr. Zawadzki, did you want to comment on the
7 retina issues?

8 DR. ZAWADZKI: If we're just talking about
9 these specific endpoints, no. But if we're talking about
10 broader issues, yes.

11 DR. BONE: Well, we're going to be asked at the
12 end to comment on the clinical benefit endpoints and the
13 potentially acceptable endpoints. I'm trying to get a
14 little discussion on those points so we can finish up
15 answering the questions.

16 Dr. Spellman.

17 DR. SPELLMAN: I agree with Dr. Seddon.

18 DR. MOLITCH: I agree.

19 DR. BONE: Dr. Feman?

20 DR. FEMAN: I agree also.

21 DR. BONE: Okay. So basically I don't think
22 anyone has recommended inclusion of items 3 and 4 under
23 that category.

24 Bear with me just a minute.

25 How about if we take a 10-minute break at this

1 point? Would that suit everybody? I think this is a kind
2 of natural stopping point before we get into the remainder
3 of the discussion, if everybody is agreeable.

4 I have six minutes after 3:00, so let's pick up
5 again in 10 minutes. Thank you.

6 (Recess.)

7 DR. BONE: Thank you. Let's resume.

8 If I understand correctly, and I'm sure I'll be
9 corrected if I don't, we've perhaps not completely resolved
10 but generally discussed the issues related to the macula.
11 What remains of the presentations this morning to be
12 discussed has to do with the proliferative retinopathy
13 endpoints. The principles, I think, again are that there's
14 been in the past acceptance of functional change, definite
15 functional change as endpoints for clinical trials, and the
16 question once again is the use of intermediate anatomic
17 changes as clinical trial endpoints and their utility.

18 Based on the comments earlier by Dr. Chambers
19 as to what the agency would like us to help with, this has
20 to do with whether these are reasonably indicative of the
21 clinical outcomes, because obviously we would want to use
22 an intermediate endpoint that was a reasonably reliable
23 indicator of what the ultimate clinical outcome would be.
24 The rationale for using these endpoints would not be to get
25 to a different conclusion, but just to facilitate getting

1 to the same conclusion about the utility of a treatment, as
2 if we had used visual acuity or some other clinical
3 outcome.

4 Dr. Wilson, please, Roy Wilson.

5 DR. ROY WILSON: I think it's an
6 oversimplification to make it appear that in the past the
7 outcomes were all functional and that now we're looking at
8 anatomical outcomes. I think anatomical outcomes were also
9 present in the past. In fact, the sheet that Wiley gave us
10 shows that at least three out of the six outcomes were
11 anatomical: vitreous hemorrhage, rubeosis, and retinal
12 detachment.

13 DR. BONE: I completely agree, but those are
14 major clinical events as well.

15 DR. ROY WILSON: I disagree. I don't think
16 rubeosis has any clinical --

17 DR. BONE: Oh, I'm sorry.

18 DR. ROY WILSON: So I just wanted to clarify
19 that it is oversimplification to make it seem like it's
20 functional versus anatomical. I think that we're looking
21 at other anatomical endpoints, but this is not something
22 that's new. It's just different anatomical endpoints than
23 what was looked at before.

24 DR. BONE: Point taken. I actually made the
25 same point myself earlier. I apologize for any

1 oversimplification this late in the day.

2 Dr. Molitch.

3 DR. MOLITCH: I just have a question about
4 what's listed here on the primary outcome variables. Does
5 this propose that they mean to include proliferative
6 diabetic retinopathy results on both of these? Or are we
7 going to accept a two-step change for eyes and three-step
8 for persons with or without the endpoint of proliferative
9 retinopathy being included?

10 DR. BONE: This is Dr. Aiello speaking.

11 DR. AIELLO: For the purposes of the discussion
12 this morning, since we were addressing agents that are
13 aimed at preventing proliferation for macular edema, we
14 were talking about a three- or two-step change on the
15 person or the eye scale, with the ultimate result being the
16 development of proliferative diabetic retinopathy. Whether
17 you apply those criteria to earlier stages is perhaps a
18 different question, as well as different types of trial
19 outcomes.

20 DR. MOLITCH: I would presume that we're trying
21 to leave things a little bit open here to encourage the
22 development of drugs, perhaps even at an earlier stage. I
23 certainly wouldn't want to limit it to this.

24 DR. BONE: So if I understand correctly, then,
25 the point you're raising, Dr. Molitch, is whether it would

1 be necessary for the, let's say, untreated patients to
2 actually even reach the point of proliferative retinopathy
3 in order for the trial to be valid if this were done at
4 such an early stage that the early changes only were seen
5 in the control group and no changes, for example, were seen
6 in the treatment group?

7 DR. MOLITCH: I'm just raising that
8 possibility, do we want to consider that in addition.

9 DR. BONE: Comments from the proponents?

10 DR. AIELLO: I think clearly we'd like to have
11 endpoints for a variety of trials. One of the perhaps
12 differentiating issues is that where proliferative
13 retinopathy develops at the end of these steps, we feel
14 that that is a very clinically important endpoint. It is
15 not a surrogate in any way. Whether or not a three-step
16 change, where you end up somewhere low in the process of
17 the non-proliferative scale, is either an interim step or a
18 surrogate may be an issue that has more differences of
19 opinion.

20 DR. BONE: Now I think I'm less clear than I
21 thought I was, but probably more correct. You're saying,
22 then, you might have either prevention of three-step
23 changes or prevention of proliferative retinopathy? I'm
24 not quite sure I'm following you here.

25 DR. AIELLO: All we're saying is that

1 prevention of a three-step change on the person scale or a
2 two-step change on the eye scale which results in
3 proliferative retinopathy would be a clear clinically
4 beneficial endpoint. We have no problem with a three-step
5 change being applied to earlier changes that would be
6 potentially of benefit, but that was not the issue we were
7 addressing.

8 DR. BONE: Thank you. That's very clear.

9 Perhaps Dr. Chambers would be good enough to
10 help us to clarify how this differs. Up to now you have
11 just not used this progression of proliferation. You've
12 had the other anatomical endpoints, and you've had acuity
13 changes. But this proliferation, per se, has not been an
14 endpoint at all. Is that a correct understanding?

15 DR. CHAMBERS: That's correct.

16 DR. BONE: Okay. And the question from the
17 agency standpoint is whether these would be regarded at
18 this point as a reliable intermediary endpoint, or whether
19 they could be with additional validation.

20 DR. CHAMBERS: That's correct. And if it's
21 felt that it is, we would like some clarification of why
22 you think it is, since most of the studies that you've
23 heard about talk about ending up in severe proliferative
24 diabetic retinopathy, not ending up in just proliferative
25 retinopathy. The actual validation, to date, goes to

1 severe proliferative diabetic retinopathy, not to
2 proliferative. Severe is part of proliferative, but it's
3 not all of what is proliferative.

4 DR. BONE: Okay. Could you discuss that point
5 a little further for me? You're saying that the
6 relationship between severe proliferative retinopathy and
7 visual acuity loss is relatively clear, but for less severe
8 proliferative retinopathy, it may not be? Do I understand
9 what you're getting at?

10 DR. CHAMBERS: Correct. The reason why there
11 is the diversity that there is in when you should be
12 treating has to do with what is clearly established, which
13 is the severe proliferative, as opposed to the various
14 recommendations made by a number of different people as to
15 whether that should be interpolated into proliferative or
16 whether it should be interpolated into severe non-
17 proliferative. We get the variation in these lower areas.
18 There is no disagreement at the severe proliferative area.
19 If we go to something less than that, we would like to know
20 what the committee is basing that opinion on.

21 DR. BONE: Okay. So really the issue here is
22 whether a change of three steps for a person or two steps
23 for an eye resulting in less severe proliferative
24 retinopathy is a sufficient change to be clinically
25 meaningful as an endpoint?

1 DR. CHAMBERS: If you take anything less than
2 severe proliferative, we would like to hear what the basis
3 for doing that is, since the studies clearly support
4 severe.

5 DR. BONE: Okay. Very good. Thank you.

6 It seems to me it would be timely to have
7 comments going around the committee, particularly the
8 retinal people, but others if they like, and then we'll go
9 back to the group who made the proposal this morning, and
10 then we'll have another round of discussion. Then we'll
11 have accomplished a lot, I think.

12 Dr. Feman, do you have a perspective on this?

13 DR. FEMAN: Yes, I do, and I'm trying to hunt
14 through the tables of the appendix material that was sent
15 to us that I think addresses some of these items, in that
16 if a person has proliferative retinopathy but not severe
17 proliferative retinopathy, the risk of having severe visual
18 loss has already been calculated.

19 Dr. Aiello, is that the slide you're going to
20 put up there? Page 28 they tell me. Appendix Item 12, I
21 think, addresses this issue. If I recall correctly, the
22 severe proliferative retinopathy that Dr. Chambers is
23 addressing is level 71 or higher. On Appendix Item 12,
24 page 28, they address the risk of progressing to high-risk
25 proliferative retinopathy if you have some level below

1 level 71. So I think the numbers already exist as to how
2 you go from one stage to the next, so I personally have no
3 problem accepting these earlier -- not surrogate, but
4 earlier endpoints.

5 DR. BONE: And I guess we didn't raise the
6 issue of non-proliferative retinopathy this morning. So
7 why don't we just go around and see if there are further
8 comments on the proliferative issue.

9 Dr. Spellman.

10 DR. SPELLMAN: I agree.

11 DR. BONE: You're agreeing with Dr. Feman?

12 DR. SPELLMAN: Yes.

13 DR. BONE: Did you care to comment on this, Dr.
14 Zawadzki? No.

15 Dr. Sloan Wilson.

16 DR. SLOAN WILSON: I basically agree also, but
17 I'm asking the question now, if we are getting further than
18 these three steps away, which ends up in severe, are we
19 putting it in a category where it will have a patient
20 population that can be analyzed? And of these, how many
21 have gotten to the point that have not had photocoagulation
22 in these lesser steps?

23 DR. BONE: If I understand correctly, we're
24 talking about being two steps back from level 65, or
25 moderate. Is that right? As a starting point.

1 DR. SLOAN WILSON: Something like that, yes.

2 DR. BONE: Okay. And your question again is?

3 DR. SLOAN WILSON: Well, my question is, will
4 you get a patient population that can fill this, that has
5 not been photocoagulated?

6 DR. BONE: I see. Perhaps we'll come back to
7 that question. Maybe the people who made the presentation
8 this morning will address that specific issue of Dr.
9 Wilson's.

10 Dr. Seddon?

11 DR. SEDDON: Would you be able to clarify the
12 question? I agree right now with these primary outcome
13 variables, but what is the question we're addressing now?

14 DR. BONE: Well, the question that Dr. Chambers
15 asked was, is there adequate justification for using mild
16 to moderate proliferative retinopathy as the endpoint here
17 in the proliferative retinopathy page, as opposed to severe
18 retinopathy? He commented that he felt that the
19 relationship between severe proliferative retinopathy and
20 visual loss was not a point of contention, but he wanted to
21 make sure that there was adequate justification for using
22 mild or moderate proliferative retinopathy as the endpoint.
23 Dr. Feman pointed to this table that we're all looking at
24 and said yes. Up to now, I guess most people have agreed
25 with the comments that they have made.

1 I guess the question is what do you think about
2 using mild or moderate proliferative retinopathy as the
3 endpoint here, where there's a two-step eye change or a
4 three-step person change leading up to that point?

5 DR. SEDDON: I think it's reasonable to include
6 all the categories of proliferative diabetic retinopathy,
7 which I assume is summarized in these endpoints as given.
8 So I would agree with that.

9 DR. BONE: Okay. Dr. Roy Wilson.

10 DR. ROY WILSON: The same.

11 DR. BONE: Okay. Dr. Cara, no comment.

12 Dr. Mindel, no comment.

13 Dr. Davidson, no comment.

14 Dr. Carney?

15 DR. CARNEY: I have a question. You're talking
16 about the use of drugs, anti-angiogenic drugs. As outcome
17 variables, this is going to be the progression to mild or
18 moderate proliferative diabetic retinopathy. That's the
19 question.

20 I don't remember what the event rate was in
21 mild to moderate proliferative diabetic retinopathy. I
22 don't know if they could define that with regard to
23 vitreous hemorrhage and retinal detachment. I think it
24 might also depend, too, on the age, the difference in the
25 diabetic populations, juveniles and adults. There might be

1 a difference, say, in anatomical changes in the eye that
2 may cause differences in posterior vitreous detachments.

3 Before I would say yes, I would want to know
4 the event rates, which I don't remember from the study, and
5 what could be some of the potential problems in juvenile
6 and adult when you look at the progression to mild to
7 moderate proliferative disease and the development of an
8 event rate in those two categories, of juvenile onset and
9 adult onset.

10 DR. BONE: So let me see if I understand your
11 concern, because I'm a person to whom this eye stuff is
12 very sophisticated as far as I'm concerned. I can only
13 stare in awe and amazement.

14 Dr. Chambers is asking us if we think the mild
15 to moderate disease is sufficiently correlated with
16 deterioration of vision to have clinical implications.

17 DR. CARNEY: Right. Clearly, the DRS defined
18 high-risk criteria as a problem for visual loss, 50 percent
19 severe visual loss, and that's what I'm referring to within
20 the study. And then the ETDRS also indicated that they
21 really didn't get into trouble until the high-risk
22 criteria.

23 DR. BONE: I see. And then Dr. Feman pointed
24 to this table that says that 63.8 or 74.7 of the mild to
25 moderate patients had reached the high-risk point within

1 five years. But the question you're raising is about other
2 events such as vitreous hemorrhage and retinal detachment.

3 DR. CARNEY: Right. I just want to know if
4 anybody remembers what the event rates were, the untoward
5 event rates in the groups that you're saying we could
6 progress to; in mild proliferative or moderate
7 proliferative, what the event rates are. What chances
8 would you be putting the patients at risk of?

9 DR. BONE: Oh, I see. So your concern is about
10 whether they should be allowed to progress.

11 DR. CARNEY: Right.

12 DR. BONE: Okay. Can someone answer that
13 question? Dr. Ferris is heading for the microphone.

14 DR. FERRIS: This is Dr. Ferris. If two-thirds
15 to three-quarters of the patients progressed to high-risk
16 retinopathy, for the most part that means they had a
17 vitreous hemorrhage. Their new vessels grew or they had a
18 vitreous hemorrhage. Some of them had traction
19 detachments. Remember, in this study they all then get
20 photocoagulation, as long as you could physically do it.

21 So I'm not sure I know how to exactly answer
22 your question, but it would look like two-thirds to three-
23 quarters develop a bad outcome and specifically get
24 photocoagulation. So it's a high-risk group.

25 In terms of vision loss, we do pretty well with

1 regard to severe vision loss, because even given this, only
2 6 percent at the end of five years in the deferred group
3 get the severe vision loss. So photocoagulation prevents
4 them from that. The question is, can you prevent the
5 development of the neovascularization in the first place,
6 and the hemorrhages and the vision loss even associated
7 with that? Somehow lost in all of the severe vision loss
8 outcomes is the fact that these patients are having
9 problems with their vision because of the recurrent
10 hemorrhages. At the end of the day they don't wind up with
11 severe vision loss, but they've had vatrectomies and
12 intermittent vision loss.

13 DR. BONE: Why don't you ask it again slightly
14 differently.

15 DR. CARNEY: I understand the severe vision
16 loss. Say you had a patient progress to mild proliferative
17 diabetic retinopathy or moderate proliferative diabetic
18 retinopathy. What would be not the chance of the patient's
19 rate of progression, but the chance of the patient's rate
20 of an untoward event, say like vitreous hemorrhage or
21 retinal detachment?

22 DR. FERRIS: Well, for vitreous hemorrhage, I'd
23 say there's a three-quarters chance. Virtually all of that
24 high risk, I would guess, is going to be vitreous
25 hemorrhage. There will be some who got to increasing

1 neovascularization and then they got photocoagulation,
2 which itself seems to me to be a bad thing, and that may
3 have prevented them from ever having a vitreous hemorrhage.
4 That's why I can't give you an exact number, because they
5 may have just had more neovascularization, gotten
6 photocoagulation, and in half of them the
7 neovascularization disappears. So they may never have that
8 bad event that you're talking about, but they have scatter
9 photocoagulation, which I assume is a bad event too.

10 DR. CARNEY: So if you are talking about a drug
11 that would allow you to progress to mild proliferative
12 diabetic retinopathy --

13 DR. BONE: That would prevent you from
14 progressing.

15 DR. CARNEY: That would prevent you from
16 progressing, but your endpoint is -- what is your endpoint
17 for treatment? It's going to be progression.

18 DR. BONE: Well, if I understand correctly --
19 and again, this is all terminology I'm not too
20 sophisticated about. But if I understand correctly, what
21 they're saying here is they would start people two or three
22 steps before mild proliferative retinopathy, and then they
23 would look at development of mild proliferative retinopathy
24 or moderate proliferative retinopathy as the event that
25 would be the endpoint.

1 DR. CARNEY: Right. My question was, in that
2 group of mild to moderate, what was the event rate? And I
3 think he just answered that.

4 DR. BONE: Yes.

5 DR. CARNEY: I mean, what I'm trying to see is
6 if you allow patients to go on an anti-angiogenic drug, to
7 be placed in a masked trial, what's the possibility of an
8 untoward event in the patients who may progress, whether
9 they're on the drug or not?

10 DR. BONE: Okay, and I think what Dr. Ferris is
11 saying is that by the time they reach that point of
12 proliferative retinopathy, 75 percent or so will have had
13 the complication. But what you're asking is, how many of
14 the people two steps back would progress to that extent?

15 DR. FERRIS: To the mild.

16 DR. BONE: That would be like the level 53a, I
17 guess. Is that what we're talking about?

18 DR. FERRIS: Roughly 50 percent of those with
19 severe non-proliferative retinopathy will progress to
20 proliferative retinopathy within a year to two.

21 DR. CARA: Why are you asking?

22 DR. CARNEY: I just want to know what risk they
23 had for vitreous hemorrhage even if they just progressed to
24 mild proliferative retinopathy.

25 DR. FERRIS: Are you worried that they're going

1 to have a bad event?

2 DR. CARNEY: Yes. That's what I'm trying to
3 figure out. In a population of patients -- say if you had
4 an adult onset diabetic who was on the anti-angiogenic drug
5 but still went to mild proliferative and had a vitreous
6 detachment, or could have the possibility of a vitreous
7 hemorrhage, what percentage of the population might be put
8 at risk?

9 DR. FERRIS: Well, the reason that we're
10 staging this at the mild end is to try to prevent them from
11 a bad outcome. In other words, to photocoagulate them
12 before high risk in that group of patients that you think
13 you need to intervene earlier. So it's a little bit like
14 the imminently threatened macula. This is a group that is
15 imminently going to be going to high-risk proliferative
16 retinopathy, and for those patients, as I said this
17 morning, particularly the Type II that I'm worried about, I
18 want to have the option of intervening early to try to
19 prevent a bad outcome.

20 It's one of the reasons in that group we were
21 hoping that you might enroll an eye rather than a patient,
22 so that the patient will have had some photocoagulation
23 early if that was a concern for you.

24 So if the concern was that we're going to be
25 letting these people go too long, that's why we didn't make

1 high-risk retinopathy the outcome variable, because we
2 think a lot of ophthalmologists aren't going to be willing
3 to wait slavishly for high-risk retinopathy. If you're
4 following a patient and they didn't have neovascularization
5 before, and now they have neovascularization, I think your
6 tendency is to say, "Gee, this ball is going downhill, I
7 want to do something before it's too late, and I'm
8 uncomfortable about waiting." That's why we tried to make
9 the threshold earlier than high-risk retinopathy, where I
10 think everybody, or virtually everybody is in agreement
11 that you should treat high-risk retinopathy. I don't think
12 I've ever had a patient get out of my office that day that
13 had high-risk retinopathy.

14 But there are a lot of patients in this earlier
15 group that when they got to that stage, I'd want to treat
16 them. The severe non-proliferative retinopathy, it's like
17 the macular edema that hasn't quite gotten to the fovea
18 yet. I'm willing to wait, but I'm only willing to wait so
19 long.

20 DR. BONE: Did that answer your question, Dr.
21 Carney? Okay.

22 Based on that information, then, the question
23 is, is the prevention of mild to moderate proliferative
24 retinopathy, is that clinically significant and meaningful?

25 DR. CARNEY: Yes.

1 DR. BONE: You're saying yes. All right.

2 Anything additional that the people who made
3 presentations this morning wanted to say about this issue,
4 or did we cover the points that you wanted to make in the
5 responses? Okay.

6 Anything additional from the committee members?
7 Anybody who didn't come in earlier who wants to make an
8 additional comment or anything like that? Dr. Cara?

9 DR. CARA: Are there any issues that would be
10 different than what we've already talked about for the
11 pediatric population?

12 DR. BONE: Yes. Dr. Ferris is going to address
13 that question.

14 DR. FERRIS: The pediatric population is pretty
15 unlikely to develop proliferative retinopathy.

16 DR. CARA: Unfortunately, we've seen patients
17 with fairly extensive retinopathy in their late teenage
18 years.

19 DR. FERRIS: Oh. Pediatric to me is little
20 children, not teenagers. Teenagers are definitely -- post-
21 puberty is when they're at risk. I would think that
22 individual sponsors might have a different point of view as
23 to whether they would want to subject minors to a new drug.
24 I'm not sure.

25 DR. BONE: That might depend entirely on the

1 nature of the drug. I think that's somewhat speculative.

2 DR. CARA: But you would be comfortable with
3 these endpoints.

4 DR. FERRIS: Oh, I think the endpoints count
5 virtually whatever the age. We have some evidence that age
6 has an effect on the outcome variable, but hopefully within
7 a study you'd find balance by age.

8 DR. BONE: Good. All right. Then it seems to
9 me, and again subject to correction if I misunderstood,
10 that we've reviewed the proposal that was made. Now, are
11 there additional proposals from members of the committee
12 about how to set up endpoints for proliferative
13 retinopathy?

14 (No response.)

15 DR. BONE: There don't seem to be any
16 additional points being suggested this afternoon.
17 Doubtless, everybody will think of one on the way home, and
18 we'll write letters.

19 Dr. Molitch.

20 DR. MOLITCH: Once we finish this proliferative
21 retinopathy, I'll re-raise the issue I raised before about
22 three-step progression to non-proliferative stages.

23 DR. BONE: Okay. That wasn't really one of the
24 things we were primarily charged with. I think it's very
25 important to discuss it, but let's take care of first

1 things first.

2 DR. MOLITCH: Fine.

3 DR. BONE: Then to summarize from the major
4 outcome variables proposed by the presenters this morning,
5 Drs. Aiello, Ferris and Davis, there was general agreement,
6 if I can summarize, on the part of the committee members,
7 led by our retinologists, that overall these seem to be
8 pretty reasonable, with a lot of comments and
9 qualifications on some individual points. But there was
10 sort of a general support. Would that be a fair summary of
11 the committee? Everybody is nodding.

12 Then we've actually been charged to review also
13 the endpoints that had been either used or considered by
14 the agency in the past, and I think what we might do is
15 kind of go through those questions in summary form. We may
16 consolidate a little bit as we go through, and then come
17 back to additional comments, such as the one that Dr.
18 Molitch wanted to raise, and then we'll wrap up. Is that
19 acceptable to Dr. Weintraub and Dr. Chambers? They're
20 nodding.

21 The questions we were asked. Firstly, is each
22 of the clinical benefit endpoints considered to be a clear
23 clinical benefit? I'll just refer everyone to page 2 of 5
24 in the FDA handout, and I'll read these very quickly as
25 people are thinking about this, and I'm just going to go

1 right around the table.

2 One, mean difference in visual acuity of at
3 least three lines; that is, doubling of the visual angle.

4 Two, change in the percentage of patients with
5 greater than or equal to three lines of visual loss,
6 greater than or equal to four, greater than or equal to six
7 lines of visual loss. So that would be a change in the
8 percentage of patients losing that much vision.

9 Third is the mean difference in the visual
10 field of at least 10 decibels.

11 Four, reduction in the percentage of patients
12 with vitreous hemorrhage.

13 Five, reduction in the percentage of patients
14 with rubeosis.

15 Six, reduction in the percentage of patients
16 with retinal detachments.

17 I guess maybe the efficient way to do this is
18 to go around to each member and ask if they agree that
19 those are clinical benefits, and then to note any
20 exceptions if they don't agree. Is that a reasonable way
21 to do it? Okay.

22 We can start with Dr. Carney, then.

23 DR. CARNEY: The clinical benefit endpoints,
24 they're fine. My only question was the use of the visual
25 field again. It's not a treatment. It's whatever drug is

1 supposed to affect the visual field or not?

2 DR. BONE: I guess.

3 Dr. Davidson?

4 Dr. Mindel? In agreement.

5 Dr. Cara? Don't disagree with anything.

6 Dr. Wilson?

7 DR. ROY WILSON: I have a question with
8 rubeosis. I think rubeosis is kind of soft, and I don't
9 know what the retinal people think, but I know that I see a
10 lot of rubeosis in my glaucoma practice that resolves on
11 its own, and I think that's consistent with the literature.
12 Rubeosis by itself can be very minimal, and it depends a
13 lot of times on how aggressive you look for it in
14 diabetics. So, maybe more for my own education, I'd like
15 to hear some more comments about the rubeosis. The others
16 I agree with.

17 DR. BONE: All right, thank you.

18 Dr. Seddon?

19 DR. SEDDON: I agree with everything. I think
20 that's a good point, Roy. It should be very well defined
21 as to what the extent of rubeosis is to have this as a
22 clinical criteria.

23 DR. BONE: Dr. Sloan Wilson.

24 DR. SLOAN WILSON: No problems.

25 DR. BONE: Dr. Zawadzki, did you have a comment

1 at all?

2 DR. ZAWADZKI: I just would like to partially
3 echo the comment made about the rubeosis because I don't
4 understand what clinical effect it has, and these are
5 clinical endpoints.

6 DR. BONE: Okay, fair enough.

7 Dr. Spellman?

8 DR. SPELLMAN: I would agree with the
9 endpoints. In response to Dr. Wilson, I would say it's
10 fairly universal for most retinal specialists to consider
11 the presence of rubeosis in patients with diabetic
12 retinopathy as an indication for panretinal
13 photocoagulation. I don't think I'm overstating that.
14 That's certainly the way it's practiced around here.

15 DR. ROY WILSON: High-risk rubeosis?

16 DR. SPELLMAN: Yes.

17 DR. BONE: Dr. Molitch?

18 DR. MOLITCH: I agree with all of them except
19 rubeosis, which I'll pass on. I don't know enough about
20 it.

21 DR. BONE: Thank you.

22 Dr. Feman?

23 DR. FEMAN: I agree with all of them, but I'd
24 like to make a couple of comments on several of the items.

25 DR. BONE: Please.

1 DR. FEMAN: Item 4, for example, is something
2 that shouldn't be happening in patients in the study. That
3 means the patient is outside the range of what's considered
4 standard care in this country, because all of the laser
5 treatments and the other things that we're doing are
6 designed to prevent that. So, sure, our goal is to reduce
7 the percentage of patients with vitreous hemorrhage, but in
8 no way could that be an endpoint. We should not have a
9 patient getting to that endpoint unless there's something
10 the matter with the study. The same thing with retinal
11 detachment. We should not have a patient getting to that
12 endpoint unless there was an error in the design of the
13 study.

14 Getting back to the question of rubeosis, I
15 forget the exact reference, but it's almost 20 years old
16 that people had demonstrated that panretinal
17 photocoagulation causes a regression of rubeosis iritis,
18 regardless of whether or not you're concerned about
19 rubeosis iritis-caused glaucoma or rubeosis iritis itself,
20 and that's why that's become a standard in many parts of
21 the country, that if an individual has photographic data
22 that a patient has rubeosis iritis, regardless of whether
23 or not glaucoma is associated with it, panretinal
24 photocoagulation is applied.

25 DR. SEDDON: Because it's a harbinger of future

1 neovascular glaucoma in those cases.

2 DR. FEMAN: Correct.

3 DR. SEDDON: That's the assumption.

4 On the other hand, I would suspect that there
5 still are patients who develop vitreous hemorrhage or
6 retinal detachment despite what we think is the most
7 adequate care.

8 DR. FEMAN: That's how we earn our living,
9 taking care of those patients.

10 DR. SEDDON: They're resistant to conventional
11 therapy, for whatever reason.

12 DR. FEMAN: Correct.

13 DR. BONE: So we're in general agreement that
14 these are clinically meaningful, but nobody thought we
15 ought to be designing trials to detect the rate of vitreous
16 hemorrhage or retinal detachment.

17 Dr. Mindel, you had an additional comment I
18 think.

19 DR. MINDEL: Yes. I was thinking, with the
20 acuity criteria and the visual field decibel criteria, you
21 have to be careful about the progression of cataracts over
22 the course of the study. That's the caveat, because if
23 there's a vitreous hemorrhage that causes a loss of acuity,
24 you've allowed for that in your criteria, but not
25 cataracts.

1 DR. BONE: Thank you.

2 The next question we were asked is does anyone
3 wish to propose additional clinical benefit endpoints
4 besides those listed and those presented this morning?

5 (No response.)

6 DR. BONE: I don't see any comments from the
7 committee. Thank you.

8 The third question on the proposed surrogate
9 endpoints that were -- we already discussed the proposed
10 surrogate endpoints completely I think already. So I think
11 we've covered that.

12 Were there additional proposed surrogate
13 endpoints besides the ones that were proposed earlier?

14 Dr. Molitch wants to raise that.

15 DR. MOLITCH: We'll come back to that.

16 DR. BONE: We'll come back to that. Fine.

17 Now, this is probably a major point of
18 discussion, and that is, looking forward, what is the best
19 means to validate the proposed surrogate endpoints? That
20 is to say, specific trial designs, duration, ultimate
21 outcomes. Let's say we had a surrogate endpoint for which
22 there was not a consensus but it seemed reasonable. How
23 would we go about trying to evaluate the clinical
24 significance of that? With some of the ones we talked
25 about, we have a lot of experience. Is this a plausible

1 question at this point? I'm looking to the retinologists
2 for guidance here.

3 DR. CHAMBERS: It's probably only practical to
4 do if you had a specific example, and the question was in
5 there if we had come up with one.

6 DR. BONE: If we had an example. Okay. So we
7 aren't trying to solve this in the general case. Fine.
8 Then I think absent such an example, we'll just go on.

9 DR. CHAMBERS: Although we have not had any
10 discussion about an event duration of any of these, of the
11 clinical endpoints, how long would it take for you to
12 believe these endpoints.

13 DR. BONE: Why don't we finish up these
14 questions, then, and then we'll take up that point and Dr.
15 Molitch's point, and then I think we'll call it a day at
16 that point.

17 I think Dr. Molitch is next.

18 DR. MOLITCH: So we're finished with all of
19 these?

20 DR. BONE: Well, I think so. The additional
21 issue is you.

22 DR. MOLITCH: I'm just raising the question
23 that I raised before. Should we think about a three-step
24 change in a person or a two-step change in an eye, or other
25 criteria similar to that that do not result in a

1 proliferative retinopathy as an endpoint for a clinical
2 trial?

3 DR. BONE: So this would be progression within
4 the non-proliferative category.

5 DR. MOLITCH: Correct.

6 DR. BONE: Great question. Comments from the
7 committee and from the others?

8 Dr. Feman.

9 DR. FEMAN: Well, as one thinks about it for a
10 moment, and we do not have a drug by name or a design or
11 structure that we're discussing at this point, but the
12 common discussion had been an anti-angiogenic agent. If
13 we're talking about an agent that is anti-angiogenic, what
14 difference does it make what happens to blood vessels that
15 are not undergoing angiogenesis?

16 Let me rephrase it. If we're looking at a drug
17 that affects angiogenesis and we're measuring things short
18 of angiogenesis that we all have an assumption will go on
19 to angiogenesis but is not necessarily angiogenesis, what
20 difference does it make? Why should we even bother
21 measuring these things?

22 DR. BONE: So you're saying this question would
23 really only apply to another type of drug.

24 DR. FEMAN: That's correct.

25 DR. BONE: Well, okay. Suppose we had another

1 type of drug?

2 DR. FEMAN: Then everything is fine.

3 DR. BONE: Okay. So you'd be happy to, for
4 example, look at the progression from mild to severe non-
5 proliferative retinopathy as being clinically meaningful if
6 we had a drug that did that.

7 DR. FEMAN: Drugs that are affecting diabetes,
8 for example, or other metabolic-type agents. But a drug
9 that is specifically aimed as an anti-angiogenic agent, we
10 don't need to measure something that is not angiogenesis.

11 DR. MOLITCH: The purpose of my point was maybe
12 Sorbinil or some other drug like that that's attacking
13 metabolic changes might very well be something we could
14 address.

15 DR. BONE: Dr. Spellman, do you have a comment
16 on that?

17 DR. SPELLMAN: No.

18 DR. BONE: Dr. Zawadzki?

19 DR. ZAWADZKI: I have a general comment. This
20 discussion is a little complex for me in the sense that we
21 have focused on the endpoints but we haven't really
22 discussed study design or confounders of study design.
23 What comes to mind is that we can come up with certain
24 endpoints, but if we don't control for certain confounding
25 factors in the design, they may not really be meaningful.

1 What comes to mind, for example, if we already
2 know that glycemic control has an impact on some of these
3 measurements and we don't control for glycemic control
4 adequately in the different arms of the study, then we may
5 see results that aren't as significant as we would like
6 them to be. That's not the purpose of this discussion, but
7 I just think it's a very important part of the whole
8 picture here.

9 DR. BONE: I think that's a good general caveat
10 in terms of overall approach to trial design. Did you want
11 to specifically address Dr. Molitch's concern about
12 possibly intervening within the non-proliferative range,
13 whether prevention of progression of mild to severe non-
14 proliferative retinopathy would be meaningful?

15 DR. ZAWADZKI: It probably is meaningful just
16 from looking at the natural history of retinopathy. Is
17 that what you mean? I mean, our goal is to sort of set the
18 clock back in various ways, and the question is what part
19 are we setting back, and where do we start?

20 DR. BONE: Dr. Chambers.

21 DR. CHAMBERS: I guess before we get too far
22 along the line, if we end up making that proposal, I'm
23 going to need some kind of discussion about why the study
24 that showed time to non-proliferative diabetic retinopathy
25 was inversely correlated with development of proliferative

1 diabetic retinopathy when we just talked about how bad
2 proliferative diabetic retinopathy is.

3 DR. BONE: I think we're getting beyond what we
4 can accomplish today.

5 DR. CHAMBERS: It goes back to it's not
6 necessarily a straight progression all the way through.

7 DR. BONE: I understand.

8 Other comments from the retinologists on this
9 issue relating to Dr. Molitch's suggestion and the concern
10 that Dr. Chambers raised? Why don't we just go straight
11 around.

12 Dr. Sloan Wilson.

13 DR. SLOAN WILSON: I guess related to Dr.
14 Molitch's question that if other things came up with other
15 types of drugs that did not necessarily fit the criteria
16 today, then that could be modified. For instance, if we're
17 talking about counting microaneurysms or these sorts of
18 things, as a method of evaluating some of these drugs, this
19 could all be changed. So I'm very comfortable with what we
20 have now.

21 DR. BONE: What do you think about this
22 supposed or published inverse relationship between
23 proliferative and non-proliferative retinopathy? Do you
24 think that means anything?

25 DR. SLOAN WILSON: I'll have to re-read it. I

1 read it to start with and I'm aware of it, but I'm not at
2 this point willing to make a statement on it.

3 DR. BONE: It's certainly not the primary focus
4 of today's meeting to solve that particular conundrum.

5 Dr. Seddon, please.

6 DR. SEDDON: I would agree that if we're
7 discussing a drug that affected vascular permeability, for
8 example, that some of these earlier endpoints would be
9 appropriate.

10 DR. BONE: Thank you.

11 Dr. Roy Wilson?

12 DR. ROY WILSON: I've got a tad bit of a
13 reservation. I think we're looking at something a little
14 bit differently. One of the agreements that we had earlier
15 today was that we probably really aren't talking about
16 surrogate endpoints but more maybe intermediate endpoints,
17 an endpoint in its own right as opposed to a surrogate.
18 The reason for that, I think, is because these endpoints
19 were so closely tied to visual loss that we felt
20 comfortable in making that statement.

21 Here I think we're really talking about a
22 surrogate endpoint as opposed to intermediate, and I think
23 that that then changes the discussion a little bit.
24 Although on the surface I would probably say it's probably
25 okay, I just wanted to bring that out, that the discussion

1 is slightly different now because now we are really talking
2 about a true surrogate as opposed to an intermediate.

3 DR. BONE: Okay. Thank you very much.

4 Dr. Cara?

5 DR. CARA: As a pediatrician and a pediatric
6 diabetes doctor, I'd like to leave the door open for
7 therapies that are designed to prevent retinopathy to begin
8 with. The issue that you just brought up I would contest
9 by saying that I think we know that if retinopathy -- well,
10 let me put it this way. Even though retinopathy to some
11 extent is spurious and somewhat unpredictable in its
12 course, we know that it does begin with non-proliferative
13 and continue on. So I think trying to make an earlier
14 impact is very important, and as we get into more and more
15 an area of prevention, especially in the younger age group,
16 I think looking at these earlier endpoints is going to be
17 very critical. It might be worthwhile discussing whether
18 even an earlier endpoint of any retinopathy at all might be
19 appropriate, or at least leaving that window open.

20 DR. BONE: Well, we can't answer all of these
21 questions today. I think we've done fairly well addressing
22 the specific endpoints we were asked to address.

23 Dr. Mindel, do you have additional comments?

24 DR. MINDEL: I like this surrogate endpoint for
25 Type I diabetes much more than for Type II diabetes. They

1 are different diseases, and the person is at risk for a
2 much longer time if he has Type I. I sort of have divided
3 feelings somewhat on that basis. I don't know if the other
4 retinal people would agree that the argument is stronger
5 for Type I. I think that came out a little bit in your
6 comment that it's a better surrogate endpoint for Type I
7 than Type II.

8 DR. BONE: Thank you.

9 Dr. Davidson?

10 DR. DAVIDSON: I may disagree with that. I
11 think that Type I and Type II diabetes are probably not too
12 different in endpoints. It's a matter of time.

13 And the other thing that is happening today
14 that I think is important for everybody to know is that we
15 have a small new epidemic of Type II diabetes in children,
16 and if we have a way of preventing the development of
17 retinopathy early on, it's quite important. Going back to
18 my first comment, for a patient, the endpoint is blindness.
19 For us, the endpoint is many things. Obviously, people
20 believe that access to care in the U.S. is excellent, but
21 access to care and access to retinologists in some parts of
22 this country, it does not exist, and it will take many
23 years for us to have that access.

24 If we can develop anything to have prevention
25 of retinopathy, I think it will solve a lot of the

1 problems. We're not going to solve everything, but I think
2 that we need to start thinking that if these interventions
3 will require pediatric-age patients, because I think it's
4 important, and adolescents, because I think we're seeing
5 pediatric and adolescents with Type II diabetes, and
6 obviously I agree with Jose that we need to really look at
7 those populations.

8 DR. BONE: Thank you, Dr. Davidson.

9 Dr. Carney.

10 DR. CARNEY: No comment.

11 DR. BONE: I think the final topic we were
12 going to address this afternoon was the question of
13 duration of trials. Obviously, this is a particularly
14 interesting question because of the early as opposed to
15 eventual findings in DCCT, giving particular concern to a
16 regulator. It has to make that kind of judgment.

17 I guess the way to start this discussion is to
18 ask the people who spoke this morning to make their
19 suggestions and then have the panel discuss.

20 Dr. Molitch, did you have something?

21 DR. MOLITCH: I just wanted to close that part
22 of the discussion and have the last word on my idea.

23 DR. BONE: Oh, pardon me, Dr. Molitch. You
24 should absolutely have the last word.

25 DR. MOLITCH: I just think that this panel and

1 the FDA should in no way give off the impression that we're
2 really against studies that may have an impact on the
3 development of new drugs that might have an impact on the
4 early development of complications, and in some ways we're
5 giving a little bit of that flavor based on the discussion
6 I think. I would really like to at least have the idea
7 that this is something that perhaps can still be
8 readdressed at some point in the future and that we are in
9 no way against the development of new medications or
10 treatments that might have an early impact.

11 DR. BONE: I'm sure that's right. I don't
12 think anybody meant to imply that. I think we were just
13 talking about some of the immediate considerations that
14 might be involved in that, rather than the long-term ones.

15 DR. MOLITCH: It's just the flavor of the
16 statement.

17 DR. BONE: Fair enough.

18 DR. CHAMBERS: And I would encourage people on
19 the committee, both now and in the future, if you think of
20 good ways to measure these types of endpoints, the agency
21 is interested in learning about them because they are not
22 things we think should just be left alone.

23 DR. BONE: Absolutely. I'm sure that's
24 everyone's view.

25 Let's come back to the wrap-up and final

1 question, which is I think the duration of trials proposed.
2 I think the simplest thing to do, if everyone's in
3 agreement, is to ask the speakers who made the presentation
4 this morning to tell us what they think about duration, and
5 then we can have comments, and then I'll summarize and
6 we'll be through I think.

7 Gentlemen, will one of you stand up and say how
8 long these trials should be?

9 DR. DAVIS: I can make one comment on the
10 length of trials. I think one of the reasons in the DCCT
11 for going to a sustained three or more step progression was
12 that we were using life table analytic methods, which don't
13 allow you to come back from the dead. So once you had an
14 event, you couldn't come back. So if there's slop in the
15 system, if there's misclassification, or if there's
16 biologic variability, this is not a very good analytic
17 method.

18 There are two ways to address that question.
19 One is to say let's have a sustained endpoint, because if
20 you go three or more steps progression and it's still there
21 six months later, the likelihood of this being either
22 biologic variability or slop in the system goes down.

23 The other thing to do is use a prevalence
24 analysis so that people can come back from the grave. So
25 if there's a three-step progression at six months and you

1 don't count that at 12 months -- you look again at that
2 same patient at 12 months, and if they've recovered, then
3 they're no longer counted.

4 So I think the duration -- it's a real
5 question, but it isn't as big a question as one might think
6 if one uses analytic methods that allow for the fact that
7 at these earlier endpoints, eyes can come back. Now, once
8 you develop proliferative retinopathy and you've been
9 photocoagulated, you don't come back. Once you develop
10 severe visual loss, very few of those eyes come back. So
11 when you use an earlier endpoint from which you can
12 recover, then you need to think about what analytic methods
13 you're going to use, and if you're going to use a life
14 table method, then you do need to use a sustained outcome.

15 DR. BONE: Well, one of the considerations in
16 the design of these trials is, first of all, sample size,
17 and secondly duration in order to have adequate power to
18 detect the therapeutic effect. But let's don't forget that
19 adequate trials also have to detect adverse effects as
20 well. That's part of what we need to have for adequate
21 exposure, enough people for long enough to have confidence
22 both in safety and efficacy.

23 I'd actually be interested, now that Dr. Davis
24 has spoken, in having both Dr. Aiello and Dr. Ferris
25 address the duration of these trials, both from the

1 standpoint of the safety and the efficacy considerations.

2 DR. AIELLO: There is one issue before I get to
3 that, and that is to further reiterate about sustained
4 change. You have to keep in mind, particularly when we're
5 looking at the latter endpoints, as some of our proposals
6 from this morning were, that once you reach those, you are
7 in most cases going to be photocoagulated, and that is a
8 one-time irreversible event. So some of this sustained
9 event is not applicable there.

10 In terms of trial duration, absolutely everyone
11 in clinical trials agrees that it needs to be adequate
12 duration to have the power to see the outcome, and also
13 then to follow those to make sure that side effects and so
14 forth are noted. The exact duration, of course, will
15 depend upon the event rates that you have in each of these
16 categories. That will depend on the power that you have
17 and how many total patients you're enrolling. That will
18 vary to some degree. But clearly, a significant interval
19 of time which has to be measured in years is going to be
20 important for these trials, and particularly if changes in
21 treatment effect are seen or not, that may want to be
22 followed further. To get additional data down the road
23 would be important.

24 DR. BONE: So I understood you to say that the
25 exposure period would be years, although you're not

1 specifying how many.

2 DR. AIELLO: That's right, because it would
3 depend upon the group that you take in, your enrollment
4 group, what their risk of progression to endpoint is, and
5 the number of patients that you're going to enroll in that
6 trial to be able to get power. But I think any trial being
7 done under shorter than a year type of duration is not
8 adequate duration at all for any of us to feel comfortable.

9 DR. BONE: And you're talking about years,
10 plural, of individual exposure, as well as years to get the
11 trial done.

12 DR. AIELLO: I'm talking about individual
13 exposure. That's a whole different issue. That's kind of
14 independent of this. I'm talking about exposure of the
15 patient to the therapy.

16 DR. BONE: So a minimum of two years? Three
17 years? Do you have any idea about that?

18 DR. AIELLO: Again, I think doing a trial for
19 less than two years would be very difficult. I would say
20 perhaps for some trials maybe two years might be adequate,
21 but you're talking two years, three years. As you move
22 earlier and earlier in these timepoints, DCCT has already
23 shown us you're probably talking four or five years.

24 DR. BONE: Thank you.

25 Dr. Ferris?

1 DR. FERRIS: I think for these proliferative
2 outcomes and macular edema outcomes that I would be
3 uncomfortable with a trial that was less than two years.
4 If you got in 1,000 patients and followed them for one year
5 and had a highly statistically significant benefit, I would
6 be concerned about adverse outcome and I would like to see
7 two to three years exposure to be certain that we weren't
8 going to have untoward outcomes.

9 With these diseases and the rates at which they
10 progress, I think from a practical point of view that's
11 necessary as well. And I agree with the comment that for
12 earlier retinopathy, I think it's very important to be able
13 to study new treatments. As I'm sure lots of you know,
14 there are reductase inhibitors that are, even now, still
15 around and being considered as potential treatments, and I
16 think we should be able to study them, and presumably you
17 would want to study them in earlier patients.

18 But the DCCT experience would tell you that if
19 you're going to get into that game, you'd better be ready
20 for four or more years because of early negative outcomes,
21 as well as the fact that there seems to be a slow
22 progression of retinopathy, and that the meaningful
23 differences start developing after three years.

24 DR. BONE: Thank you. So it seems to be that
25 the speakers are recommending a two- to three-year minimum

1 exposure, and they suggest it might be longer if the
2 patients were very mildly affected to begin with.

3 Comments from the committee? I'll just go
4 around the table. Does anybody have a different view?

5 Dr. Freeman?

6 Dr. Molitch?

7 DR. MOLITCH: Similar.

8 DR. BONE: Dr. Spellman?

9 DR. SPELLMAN: No difference.

10 DR. BONE: Dr. Zawadzki?

11 Dr. Wilson?

12 Dr. Seddon?

13 DR. SEDDON: The same.

14 DR. BONE: Dr. Cara?

15 Dr. Mindel? Dr. Mindel has a different view.

16 DR. MINDEL: I think if the data can be
17 analyzed at periodic intervals with the study still
18 remaining masked, there are ways of doing that so that you
19 can really, every year, analyze the data. If the drug is
20 effective, you do it, you find it out. But the question
21 is, how long will the drug company keep funding the study
22 if there are no positive results? If there are negative
23 results, it will show. If the drug is bad or if it's
24 better, if you analyze it arbitrarily in a year or two
25 years, or whatever.

1 So I think it's not really so much a question
2 for us. It's a question for the drug companies.

3 DR. BONE: What would you regard as a minimum
4 exposure to have an adequate evaluation, a minimum exposure
5 for subjects? Would you agree with the two- to three-year?

6 DR. MINDEL: I think it's really a guesstimate,
7 because we don't know how effective a drug is. Some drugs
8 are very effective and some drugs are minimally effective.
9 It may take one drug five years to show its benefit,
10 another 10 years, another two months.

11 DR. BONE: Thank you.

12 Dr. Wilson, we were just commenting on if there
13 were any members of the committee who had a different view
14 from the speakers, who said that they would expect a trial
15 to be a minimum of two and perhaps longer years per
16 subject.

17 DR. ROY WILSON: I'm in total agreement.

18 DR. BONE: Dr. Davidson?

19 DR. DAVIDSON: The safety of the drug is
20 important, and I think that to do a one-year study is
21 unfair. But you also need to look at the staging of the
22 patients. I think that a drug like that is very promising
23 and we will need to have trials at different stages of
24 retinopathy. Whoever designs the trial will need to design
25 it with the objective to see points at a given time. Then

1 maybe some trials will be two years, maybe some will be
2 three years, some will be six years.

3 DR. BONE: Dr. Carney?

4 DR. CARNEY: No comment.

5 DR. BONE: Well, there seems to be a reasonably
6 consistent view on this point.

7 Are there any further comments before we
8 summarize and finish?

9 (No response.)

10 DR. BONE: It seems that we've covered quite a
11 bit of ground today. We've had a review by Dr. Chambers of
12 what the agency has regarded and has considered but not yet
13 accepted as clinical endpoints, and some recommendations
14 about endpoints with clinical implications which we might
15 regard as intermediate endpoints by the speakers.
16 Generally speaking, the committee has regarded the
17 recommendations from the speakers as reasonable, with a
18 number of valuable comments and suggestions, and overall
19 there has been a view that a trial period of two to three
20 years exposure per subject is probably a minimum in order
21 to have a thorough evaluation of a new drug, but with
22 several comments that this might be somewhat dependent on
23 the exact nature of the drug, of course.

24 I think that we reviewed the questions and
25 discussed them pretty thoroughly as well, and I think we're

1 ready to adjourn.

2 Dr. Weintraub?

3 DR. WEINTRAUB: Just a short thank you from me.
4 I wanted to thank you for your perspective. It came out
5 very well in the discussion.

6 Now, as the regulators, we're going to
7 integrate, we have to integrate the positions and the ideas
8 of clinicians, whether they're academicians or people
9 treating real people in the real world. I only say that
10 because I used to be an academician myself.

11 We integrate also the patient's view, the drug
12 developer's view, and it's important to have all of these
13 things so we can make an adequate risk/benefit judgment. I
14 use the word "judgment" advisedly. It's not a decision,
15 because a decision is something that's made that's easy to
16 make. This is a judgment, and it's sometimes very hard.

17 Then I wanted to say something about this type
18 of meeting, where we didn't discuss a particular drug but
19 we asked you to help us think about the subject. I like
20 these kinds of meetings because you get really great
21 discussion and it stimulates all of us to think. Of
22 course, it's not bad also for you to discuss a particular
23 drug, but I like this kind of meeting more.

24 In many ways, you are our advisors. Some of
25 you who consult for drug companies know that you can be a

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