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CENTERS FOR MEDICARE AND MEDICAID SERVICES

Medicare Coverage Advisory Committee

September 9, 2003

Holiday Inn Inner Harbor

Lombard and Howard Street

Baltimore, Maryland

Panelists

Chairperson
Ronald M. Davis, M.D.

Vice-Chairperson
Barbara J. McNeil, M.D., Ph.D.

Voting Members
Wade M. Aubry, M.D.
Robert H. Brook, M.D., Sc.D.
Anne B. Curtis, M.D.
Susan Bartlett Foote, J.D., M.A.
Steve N. Goodman, M.D., M.H.S., Ph.D.
Karl A. Matuszewski, M.S., Pharm.D.
Margaret A. Piper, Ph.D., M.P.H.
Rita F. Redberg, M.D., M.Sc.
Paul J. Wallace, M.D.

HCFA Liaison
Steve Phurrough, M.D., M.P.A.

Panelists (Continued)

Consumer Representative
Linda A. Bergthold, Ph.D.

Industry Representative
G. Gregory Raab, Ph.D.

Guests
Alan M. Garber, M.D., Ph.D.
Oliver D. Schein, M.D., M.P.H.

Executive Secretary
Michelle Atkinson

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

PANEL PROCEEDINGS
(The meeting was called to order at 8:07 a.m., Tuesday, September 9, 2003.
DR. DAVIS: Good morning everyone and welcome to this meeting of the Medicare Coverage Advisory Committee. I am Ron Davis, the new chair of the committee, and we're going to make some introductions of members of the committee, but before we do that, I wanted to turn it over to Michelle Atkinson, executive secretary of the committee, who is going to make some opening remarks and then we will proceed with the agenda.
MS. ATKINSON: Good morning and welcome, committee chairperson, members and guests. I am Michelle Atkinson, an executive secretary for the Medicare Coverage Advisory Committee. The committee is here today to discuss and make recommendations concerning the quality of the evidence and related issues for the use of ocular photodynamic therapy with verteporfin in routine clinical use in the population of Medicare beneficiaries who have age-related macular degeneration and occult with no classic choroidal neovascularization.
The following announcement addresses conflict of interest issues associated with this

meeting and is made part of the record to preclude even the appearance of impropriety. The conflict of interest statute prohibits special government employees from participating in matters that could affect their or their employer's financial interests. To determine if any conflict exists, the Agency reviewed all financial interests reported by the committee participants. The Agency has determined that all members may participate in the matters before the committee today.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products or services they may wish to comment on. This includes direct financial investments, consulting fees, and significant institutional support.

Now I would like to turn this meeting other to Dr. Steve Phurrough.

DR. PHURROUGH: Thank you, Michelle. I am Steve Phurrough, I am the director of the Coverage and Analysis Group at the Centers for Medicare and Medicaid Services, and I want to welcome the panel and thank them for their willingness to serve in this

particular capacity and for the presenters, both the scheduled presenters, the requestors, the public presenters, we appreciate your interest and your willingness to be here and assist us in this today. The panel has a very complicated and very difficult role today in looking at a very difficult problem that we have in clinical medicine in the United States today, and we have some very well respected folks who are going to be discussing the issues with us. We have our typical clear evidentiary questions where we want to know about the strength of the evidence and then what that evidence shows, and then we will have some discussion questions around particular policy issues that are of interest around this particular issue.
Dr. Davis will ask the panel members shortly to introduce themselves and disclose their conflicts of interest. I would like to make known to the public that we have in fact had a fair amount of discussion about the panel selection, there have been some discussions about conflicts of interest with the panel members. We have gone through a very detailed process in the Medicare office as we usually do, to ensure that the conflicts of interest are not such that they prevent the panel members from

participating.
If there are members of the public who would like to make comments on that for the record, you will need to register for the open public comment period time and you can make the comments at that time.
With that again, I thank the panel for their participation and I wil turn it over to Dr. Ron Davis, who is the chairperson for the meeting.
DR. DAVIS: Thank you very much, and I would like to just start out by thanking CMS for the opportunity to chair this distinguished committee and for making sure that there is a vice chairperson designated, Dr. Barbara McNeil. In case I falter at any moment, she will help me out.
I would like to also acknowledge the outstanding leadership that Dr. Hal Sox provided to the Medicare coverage committee for its first four years of its existence, and he established a precedence for running an efficient meeting and making sure that we perform all of the duties that were asked of us, and I will do my best to follow in his shoes.
In terms of the charge to the committee, I think it has already been alluded to and I think the

members of the committee are already familiar with the fact that we have a number of questions that we're going to be asked to decide on, voting questions that have been made available to us and to other interested parties, as well as some discussion questions. And obviously after we hear all of the material that will be part of the agenda, then we will do our best to make decisions on those voting questions.

The agenda is available not only to the committee members but to all interested parties who are here in the audience, and so anybody who doesn't have a copy of the agenda will be able to obtain one, I believe, with the CMS staff who are here at the meeting.

At this point let us go around the table and have each member of the committee introduce himself or herself, and I would ask you as we have done in the past to indicate your institutional affiliation and any potential conflicts of interest that you might have.

Once again, I'm Ron Davis. I am director of the Center for Health Promotion and Disease Prevention at the Henry Ford Health System in Detroit. I will just mention one other significant

role that I play which I don't believe is a conflict of interest but I will mention it nonetheless, and that is, I am a member of the board of trustees of the American Medical Association. Barbara.

DR. McNEIL: I am Barbara McNeil. I am head of the Department of Health Care Policy at Harvard Medical School and a radiologist at the Brigham and Women's Hospital. I do not believe I have any conflicts relevant to this discussion.

DR. BROOK: Robert Brook, I'm at Rand and UCLA, and I don't think I have any conflicts.

MS. BARTLETT FOOTE: Susan Bartlett Foote. I'm the head of health services research and policy at the University of Minnesota.

DR. MATUSZEWSKI: Karl Matuszewski, director of the Clinical Knowledge Service at the University Health System Consortium and I don't have any conflicts of interest.

DR. CURTIS: Anne Curtis. I'm a cardiologist at the University of Florida in Gainesville, and I have no conflicts.

DR. WALLACE: I am Paul Wallace. I am the executive director of the Care Management Institute for Kaiser Permanente, and I don't have any conflicts of interest in this matter.

DR. PIPER: Margaret Piper, with the Technology Evaluation Center the Blue Cross and Blue Shield Association. No conflicts.
DR. RAAB: Greg Raab. I'm an independent health policy consultant. I have no conflicts.
MS. BERGTHOLD: Linda Bergthold. I'm a consultant with Watson Wyatt Worldwide. I don't have any conflicts. However, my father does have macular degeneration, so I have an intense interest in the subject.
DR. GOODMAN: I am Steve Goodman. I'm a biostatistician and epidemiologist at Johns Hopkins University. I have no financial conflicts. I was consulted by CMS on their interpretation of the evidence in preparation of their March 28th memo, although I didn't participate in the decision process.
DR. REDBERG: I am Rita Redberg. I'm a cardiologist at the University of California San Francisco Medical Center and I have no conflicts.
DR. AUBRY: I'm Wade Aubry, an internist endocrinologist at the University of California San Francisco, and also a senior advisor for the Health Technology Center in San Francisco, which is a nonprofit technology forecasting organization. I

have no conflicts of interest.
DR. SCHEIN: My name is Oliver Schein. I'm a professor of ophthalmology at Johns Hopkins, the Wilmer Eye Institute. I don't believe I have any conflicts. I do have a research grant from CEBA to study adverse events associated with extended wear contact lenses.
DR. GARBER: I'm Alan Garber. I'm a staff physician with the Department of Veterans Affairs and a professor of medicine at Stanford. I have no conflicts.
DR. BROOK: Dr. Phurrough.
DR. PHURROUGH: Just to clarify for the panel and the public the status of the panel members. Dr. Schein and Dr. Garber are guest panel members, they are to assist the panel members in their deliberations, they are nonvoting members. Linda Bergthold and Greg Raab are the industry rep and consumer rep, and are here to take part in the discussion but they are nonvoting members. The remainder are voting members. Dr. Davis is a nonvoting member unless he needs to break a tie.
DR. DAVIS: Thank you. Let us proceed then with the next item on the agenda, which is the CMS presentation of request and voting/discussion

questions.
MR. CAPLAN: Good morning. Thank you, Chairman Davis, panelists, invited guests, and members of the public. On behalf of the Centers for Medicare and Medicaid Services, welcome to today's Medical Care Advisory Committee meeting on verteporfin for age-related macular degeneration or AMD. Today's analytic team includes Dr. Marc Stone as the lead medical officer, myself, Stuart Caplan as the lead analyst, and the MCAC executive secretary Michelle Atkinson, who you know well.
I would like to also thank my other colleagues at CMS who worked diligently to help prepare today's presentation. The presentation today includes information on age-related macular degeneration in the Medicare population, a history of Medicare coverage of verteporfin, review of MCAC voting questions and discussion questions, a presentation by Dr. Charles P. Wilkinson, and a CMS review of evidence and data analysis.
The panel has received the following materials, all of which are publicly available. They include full text articles of the TAP and VIP trials, information on FDA status for verteporfin, copies of all articles reviewed in this analysis, along with an

evidence summary, trial protocols, and the voting and discussion questions for the panel.
Age-related macular degeneration is the leading cause of legal blindness in Americans over the age of 65. The National Eye Institute estimates that there are 165,000 new cases of AMD each year. Of these, 90 percent or about 150,000 are diagnosed with dry or nonexudated AMD. 10 percent, or approximately 15 percent have the wet or exudated form of AMD. The exudated form, which causes more rapid and severe vision loss, is the focus of today's meeting. The estimated prevalence of AMD in Americans 75 years of age or over is 7.5 percent.
There is no cure for age-related macular degeneration. There are, however, a number of available treatments. Photodynamic therapy is by far the most widely used treatment with the greatest amount of published peer reviewed evidence. Laser photocoagulation relies on heat to seal leaking choroidal neovascular lesions but it causes thermal damage to retinal tissues. As a result, its use for subfoveal neovascular lesions has largely been abandoned. Transpupillary thermotherapy also uses a thermal laser but at lower intensity to seal leaking vessels. Results of the thermal transpupillary

procedure for CNV study should be released in early 2004. Surgical therapies being evaluated include macular translocation surgery and other surgical interventions. These procedures require meticulous patient selection and highly skilled surgeons. Anti-angiogenesis therapy is aimed at inhibiting growth of subfoveal blood vessels. We will learn more about Phase II and Phase III trials of anti-angiogenesis therapy from Genaera and Genentech later today.

Except for OPT with verteporfin, Medicare has not made national coverage determinations for other AMD therapies. On April 12th, 2000, the FDA approved verteporfin for predominantly classic age-related subfoveal choroidal neovascularization or CNV, as determined by fluorescein angiography. On August 22, 2001, the FDA approved verteporfin for predominantly classic subfoveal CNV related to pathologic myopia and presumed ocular histoplasmosis. The use of verteporfin for occult and no classic AMD is an off-label use.

We will focus our attention today on two clinical trials of verteporfin known as TAP and VIP. TAP is the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy Study Group,

and of interest today are the TAP I and TAP II trials. The VIP is Verteporfin in Photodynamic Therapy Study Group and today we will focus on the VIP II trials.

I would like to provide a brief history of Medicare's coverage decision memoranda which analyzed issues related to verteporfin for AMD. Prior to November 8, 2000, there were not national coverage determinations for treating AMD and as such, the AMD treatment was strictly at contractor discretion.

Medicare has issued three decision memoranda regarding photodynamic therapy with verteporfin. In the decision of November 8, 2000, CMS announced its intent to cover ocular photodynamic therapy with verteporfin for AMD patients with predominantly classic subfoveal choroidal neovascularization. That is, where the area of classic CNV occupies greater than 50 percent of the area of the entire lesion as determined by fluorescein angiography. Other uses of OPT with verteporfin were specifically noncovered. These included patients with minimally classic CNV, that is, where classic CNV occupied less than 50 percent of the area of the lesion. Also noncovered were lesions outside of the fovea, patients unable to obtain a fluorescein angiogram, and patients with

atrophic or the dry form of AMD. This decision was based on the TAP study group data.
On October 17, 2001, CMS announced its intent to issue a national coverage determination to expand coverage of ocular photodynamic therapy for AMD patients with predominantly occult subfoveal CNV, that is, where the classic CNV occupies less than 50 percent of the entire lesion.
After posting that decision, CMS discovered new issues concerning data from the VIP II trial upon which we based our analysis. On October 29 of 2003, CMS announced that it would not implement the October 17 decision -- I'm sorry, that's October 29 of 2001. CMS announced that it would not implement the October 17 decision memorandum. CMS believed that further review was needed to fully understand the new concerns raised regarding clinical trial data in VIP II. As a result, CMS generated internally a request for reconsideration of this indication of OPT for occult AMD and it remained noncovered.
On March 28, 2002, CMS announced its intent to reaffirm that noncoverage policy for predominantly occult lesions. On July 25th of this year, CMS opened a reconsideration of our national

noncoverage policy and we are here today as part of that reconsideration process.

The panel has had an opportunity to review materials related to verteporfin for AMD. After hearing the public comments and scheduled commentaries presented here today, the panel will be asked a series of voting and discussion questions. The voting questions address specific evidentiary issues related to verteporfin therapy. The discussion questions, on the other hand, relate more to policy and societal issues and do not involve evidentiary burdens.

Panel Voting Question 1 is as follows: Is there adequate evidence to draw conclusions about the net health outcomes, that is, whether or not the risks and benefits of treatment outweigh the risks and benefits of non-treatment, of ocular photodynamic therapy with verteporfin in routine clinical use in the population of Medicare beneficiaries who have age-related macular degeneration and occult with no classic choroidal neovascularization?

We have asked the panel to use MCAC's own categories of effectiveness which I will review with you after looking at voting question two.

Question Number 2 is as follows: If the

panel answers the first question affirmatively, does the evidence demonstrate that OPT with verteporfin treatment improves net health outcomes in treating age-related macular degeneration with occult and no classic choroidal neovascularization, and if so, what is the size of the benefit in patients receiving such treatment?
The MCAC categories of effectiveness are listed on the slide and they range from breakthrough technology to not effective.
Let's move on to the panel discussion questions.
Discussion Question Number 1: Neither the TAP nor VIP trials address cessation of verteporfin therapy. Under what circumstances should treatment be discontinued?
Discussion Question Number 2: What additional research studies might be useful in clarifying outcome measures, subgroups of patients most likely to benefit, duration of treatment, and other aspects of the use of verteporfin in the Medicare population?
Panel Discussion 3 is as follows: If the evidence demonstrates that OPT with verteporfin improves net health outcomes, does the size of effect

of treatment, from a societal perspective, outweigh the clinical risk and costs of its widespread use that would be created for patients in the Medicare program?

I would now like to introduce to you Dr. Charles P. Wilkinson, who will present a clinical overview of AMD as well as provide us with his insights and opinions on treating this disease.

Dr. Wilkinson.

DR. WILKINSON: Good morning, panel members. I'm Pat Wilkinson, I'm the chairman of the department of ophthalmology at Greater Baltimore Medical Center. I am a professor in the department of ophthalmology at Hopkins, part-time there. We're gathered this morning to discuss PDT or photodynamic therapy with the drug verteporfin for age-related macular degeneration or AMD.

DR. PHURROUGH: Excuse me, Dr. Wilkinson. Could you please tell us and the public what some of the issues that you have, organizations you work with and so forth?

DR. WILKINSON: Yeah, I was coming to that. That's on my third slide. I'm going to give a brief overview of the disease, which I was asked to do, and then following Dr. Stone's presentation, look

at some additional information, and then finally present my personal views on PDT for AMD. Your question was related to my conceivable potential conflicts. I want to disclose that I'm speaking on my own behalf as a vitreal retinal specialist with interest in macular degeneration. I specifically am not speaking as a representative of or on behalf of a subspecialty society, medical organization or pharmaceutical company. My words are intended to represent my personal views on this topic.

Nevertheless, virtually all retinal specialists belong to subspecialty societies and I'm fortunate to be a member of a few. I'm a member and on the board of trustees of the American Society of Retinal Specialists. I am a member and president elect of the Retinal Society, and I am a member of the Macular Society. In addition, I should disclose, I was chairman of the American Academy of Ophthalmology's preferred practice pattern retinal panel from '92 to 2001. And finally, I am currently serving as a member on the data safety monitoring committee of a small ongoing study of a combination of steroids and PDT for macular degeneration. This is a study that's privately funded without support

from industry.
AMD is currently a very frustrating problem, as you all know. It seems to be occurring in almost epidemic proportions in our relatively healthy but aging population and optimal therapy remains unavailable. Our results to date are disappointing.
A brief overview of the disorder should first note that some degree of macular dysfunction is normal as we reach our eighth and ninth decades when few have macular function of teenagers. The precise definition of so-called early AMD is debated. What some may call early AMD, others might term normal aging changes. Still, any typical morphologic change in the macula that is associated with reduced vision would correctly be regarded as early disease.
The macula, which is roughly outlined by this white circle, provides us with our good sharp central vision. Vision to the side of exactly what we're looking at is never as sharp as precise central vision. If one looks at this photograph of books, all the titles seem to be in focus and yet, if one examines what he or she is really seeing, it's actually a relatively central zone, such as that represented by that scribbled dark circle, and if

gaze is deliberately maintained on this circle, the titles to all sides are literally not as well seen. So this photograph is actually a more accurate example of what we actually see. Only the central portion of our visual field is highly focused and all things to the side are less well seen. The true central clear zone is obviously somewhat smaller and obviously round, and with less distinct borders. And if macular function is lost, nothing is literally in optimal focus, even though peripheral vision remains normal.

AMD is classically classified as dry or wet, as Dr. Caplan said. Dry changes are by far the most common in macular degeneration and are associated with pigment changes. Some degree of dry AMD almost always precedes the wet form. This is a color photograph of a normal macula. The pigmentary pattern is quite homogeneous. This photograph depicts significant alterations in the pigmentary pattern of the macula. And although the patient might have excellent vision, he or she is at genuine risk for a major loss of central vision in the future.

Wet AMD is usually due to the growth of abnormal blood vessels beneath the retina. In a

manner similar to Bermuda grass emerging from cracks in the sidewalk, these vessels grow from tissue beneath the retina, which is termed the choroid, into the space beneath the pigmented layer of the retina, under the century retina itself or both. These abnormal vessels are termed choroidal neovascularization, or CNV. The wet form of AMD is now termed neovascular AMD and is responsible for 90 percent of legal blindness due to AMD.

This cartoon that with apologies, was stolen from someone, illustrates these abnormal vessels entering the space beneath the pigmented layer of the retina. This pathology micrograph courtesy of Dr. Dick Green illustrates the same phenomenon.

CNV has become defined on the characteristics that are present on a classic diagnostic study, fluorescein angiography. Fluorescein angiography is a test in which fluorescein dye is injected into a vein and the circulation of the eye is then photographed with appropriate filters inserted in front of both the flash source and the film. The highlights of the normal retinal vessels and the pigment epithelium of the retina are quite obvious. If the pigment is

abnormal or if CNV exists, there are many characteristic differences. Over the past two decades the classification of CNV has been modified to reflect the latest consensus opinion regarding these vessels. Currently there is agreement about classifying CNV as classic, occult, or a combination thereof. For the purposes of studies regarding the use of PDT, neovascular lesions that exhibit greater than 50 percent classic CNV have been termed predominantly classic. The so-called classic characteristics of CNV include a lesion that hyperfluoresces early in a very discrete and well demarcated area; dye slowly accumulates in this site.

This is a photograph of an eye with severe AMD due to CNV in spite of the fact that it might superficially look fairly normal. The early phase of the angiogram demonstrates an obvious lesion that leaks and that is well demarcated.

There are typical changes as the study progresses, and this pattern is typical of classical CNV. This is a later stage of leakage.

Here is another clinical photograph with less subtle changes and a similar pattern is observed, and this is later.

Occult CNVs are another story. In these situations there are signs of CNV, but even though the presence of CNV is apparent, the precise location is not. It is important to recognize that the understanding of fluorescein findings indicating occult CNV has evolved over the past decades. The precise reasons that these CNVs are different angiographically remains unknown, but it may be due to a combination of factors including differences in CNV permeability, dye rapidly filling the space beneath the retina, other material in the space beneath, and unknown factors.

This is a photograph of an eye with a neovascular CNV. The early phase of the angiogram demonstrates no classic lesions. Later in the study there are obvious areas of leakage but the precise dimensions of the lesion are not so apparent. And the late phase clearly indicates leakage but the precise location remains unknown.

Another case with some protein and lipid beneath the retina, the early phase of the angiogram demonstrates some hyperfluorescence without well defined borders, and the late phase is similarly no more helpful. The features do indicate occult CNV, even though I can remember days in the past when this

was not so apparent. We do see what we know. A red-free photograph of another case. Some early hyperfluorescence, and a late hyperfluorescence showing a much wider area of involvement. Most patients with CNV have components of both classic and occult CNV, and the size of the classic component has been the critical factor in determining CMS coverage. Currently, more than 50 percent of the lesion must be classic to qualify for such coverage, and these lesions are termed predominantly classic. This is a case with some obvious blood, a very common associated finding. The early phase of the angiogram demonstrates an obvious area of classical change right there, but there is also some hyperfluorescence unassociated with the classic component, and the blood blocks a portion of the possible leakage. The leakage is less well defined in the nonclassic portion of the lesion as the study progresses. The late phase demonstrates that occult CNV appears to occupy at least or perhaps more than 50 percent of the lesion. Another case, lousy color photograph. In this instance there is a tiny area of early leakage

that some might term classic or potentially classic, but as the study progresses, there's a large area of more subtle and ill-defined hyperfluorescence consistent with occult CNV. As the study progresses further, the ill-defined portion is clearly more extensive but the small area of early leakage remains identifiable and might be interpreted as classic. It should be emphasized that the differentiation between classic and occult can be both difficult and debatable, but this lesion is clearly not predominantly classic.

As Dr. Caplan mentioned, classic treatment for CNV involves thermal laser therapy of burning the retina. I won't spend any more time on that. It's not optimal because you burn up what you're trying to save when you treat subfoveal lesions.

Photodynamic therapy, on the other hand, offers a potential means of destroying or in some way modifying the choroidal neovascularization without major damage to the overlying retina. This is because PDT causes a photochemical reaction in these abnormal vessels rather than a thermal burn.

So, I'm going to stop right now temporarily and have Dr. Stone come up and provide some more information.

DR. STONE: Thank you, Pat. Scientific evidence considering the use of ocular photodynamic therapy with verteporfin is concentrated in two studies.

In the TAP trial, which is, the TAP investigation is a pair of multicenter randomized placebo-controlled clinical trials that were specifically conducted to determine if photodynamic therapy with verteporfin would safely reduce the risk of vision loss in patients with subfoveal classic CNV caused by AMD.

And I want to correct something that Stuart said, he misspoke slightly talking about TAP I and TAP II. Those are the names of the published papers, the reports. Their was no TAP I trial and TAP II trial. Similarly, there was no VIP II trial. There was a VIP Report Number II which concerned choroidal neovascularization from age-related macular degeneration. The first paper concerned pathologic myopia.

In the TAP trial, the study enrolled 609 subjects in 22 ophthalmology practices in North America and Europe. Subjects were randomized in a two to one ratio of active drug to placebo, stratified by visual acuity and center. Assignment

was masked from patients, doctors, vision examiners, and angiogram readers. The published reports from the TAP trial showed a statistically significant difference in the proportion of subjects who lost less than 15 letters of visual acuity at one year after initiation with treatment. In the subgroup with predominantly classic CNV, that is, CNV constituting 50 percent or more of the lesion, the observed difference was even stronger. But in the complementary subgroup, those with classic CNV comprising less than 50 percent of the lesion, there was no apparent difference. As a consequence, ocular photodynamic therapy with verteporfin for age-related macular degeneration was approved by the FDA and covered by Medicare only for predominantly classic CNV. The published results gave no explanation for the difference in effect, but it appears to be due to confounding with differences at baseline visual acuity. There is no difference in effect once these differences in baseline visual acuity are accounted for, and you can see that analysis in page 34 of the statistical appendix. A subsequent paper showed the results at 24 months and those were very similar. These are all

subjects. This is the group with predominantly classic CNV, again, a significant difference. And with minimally classic CNV, again, not much difference seen in 24 months.

The VIP trial enrolled AMD patients who were not eligible for the TAP trial, that is, subjects who did not have classic CNV or had classic CNV with such good visual acuity that they didn't want to use a new drug on them because there were still some safety concerns. Also in the VIP trial, subjects with pathologic myopia were studied simultaneously in an essentially separate trial with separate randomization, primary outcome variable and statistical analysis.

In the VIP trial there were 339 AMD subjects. Randomization and masking procedures were the same as for the TAP trial. Unlike the TAP study, the one-year results of the VIP study were not published until the 24-month results were also available.

The primary results, loss of 15 letters of visual acuity at one year showed little difference. The paper reports results at 24 months that would be considered statistically significant. The paper also published similar two-year results for the subgroup

with only occult CNV. In addition, the paper featured results for a 30 letter loss of visual acuity in the occult only subgroup. This is how the results of this trial were presented to the ophthalmology community. In a little while I will come back and talk about what was left out of this presentation, but first I would like Dr. Wilkinson to talk about his reaction as a practicing retinal specialist to these trials as they appeared in the literature.

DR. WILKINSON: Photodynamic therapy with verteporfin has been demonstrated to be of value for predominantly classic CNV and as you heard, CMS approved payment for predominantly classic lesions in November of 2002. PDT does not appear to be sufficiently effective for lesions with only some classic features that occupy less than 50 percent of the lesion.

It was interesting and perhaps surprising to many that subsequent data demonstrated that PDT is of some value for lesions that are 100 percent occult. Since PDT works for predominantly classic lesions, but not for lesions that contain some classic but are predominantly occult, some did not expect effectiveness for pure occult.

The key data demonstrating the treatment benefit for pure occult lesions are pictured on this slide. Note that there are not significantly statistically significant favorable outcomes at 12 months but at 24 months moderate visual loss was less significant in the treated eyes, and the reduction of severe visual loss on the right was even more significant. So this column furthest on the right is particularly compelling, and these data represent the primary reasons that most physicians do recommend therapy for these lesions.

I'm going to digress for a moment. This is a standard Snellen chart, one that you've all seen, the type that we use in our offices. But this chart is not appropriate for research studies, so this is the current standard vision chart used in most research trials. It is called the ETDRS chart and is based on the chart originally created by Bailey and Loebe.

In these studies using this chart, moderate vision loss was defined as the loss of three lines on this chart, and so-called severe vision loss was approximately the loss of six lines or more. This is an attempt to demonstrate the average visual acuity in patients with pure occult lesions who

entered the study. Due to the fact that the chart was used at two, rather than four meters, the patients could actually see further down the chart because it was closer, but the average entering vision of approximately 20/50 is accurately depicted. This slide is an attempt to represent 12-month follow-up average vision. Average vision was lost in both untreated eyes, and they are represented in pale green and there are more of them, than in treated eyes represented in pale pink, and you can see a modest difference. Again, note that the letters lost in this diagram are only half of the true number of letters lost because the chart was 50 percent closer to the patient. Now this slide represents data at 24 months. Again, a difference is observed, both of them got even worse, but there is a difference favoring treated eyes at 24 months that was statistically significant. If you look at this in a grosser fashion, you can say if you have some of your macula knocked out it might be like this, this is even worse, this is even worse, and the prevention of severe visual loss did appear to be significant in the data I showed you.

So this table demonstrating a significant benefit at 24 months remains the keystone for a recommendation to treat purely occult lesions. The consensus of opinion in the retina community is that PDT is indeed recommended for most acute small subfoveal lesions that are 100 percent occult. I don't think anyone is overwhelmed with the success rate of this form of treatment, but it does appear to be better than nothing.

As was mentioned at the onset, this meeting is being held to reconsider the current position of CMS, which is that coverage for those occult lesions is denied. Prior to this meeting, CMS requested additional data from the sponsor of verteporfin in an effort to learn more about the so-called observed effect, if this effect was truly due to the use of PDT, if patient attrition affected the significance of the data, and to consider the possible reasons that the biologic effects of treatment appear to be different for different components of subfoveal CNV.

New Kaplan-Meier curves were subsequently generated for moderate and severe visual loss, and also for time to reach 20/200 or less visual acuity. The new tables generated following removal of

patients in which so-called last observation carried forward was used as an ultimate end point are rather similar to the original, with statistically significant favorable results occurring at the 24-month follow-up period, particularly in regard to severe visual loss.

This presentation will be concluded with a sequence of my personal impressions regarding the use of PDT with verteporfin for subfoveal pure occult CNV. As mentioned earlier, these opinions are mine and are not intended to represent the opinions of any other individuals or organizations.

First, the additional review of the data does not alter my views about the fact that treatment appears to be of some value. I want to re-emphasize that I'm a clinician and not a biostatistician. I've interpreted the published data and their apparent significance to me as a clinician.

Secondly, in spite of so-called statistical significance and value, the real life clinical outcomes are limited. PDT does appear to do something that alters the behavior of CNV. The fact that a significant value is not observed at 12 months is consistent with my impression that the overall value is limited. Progression of visual loss

continues in both treated and untreated eyes and most ultimately become legally blind. There are very few contented patients who have had their eyes treated. Still, the rate and extent of this decline and particular severe decline are significantly lower in treated eyes.

Pure PDT will not remain as the best therapy for this form of AMD because its outcomes are limited. There are several potential alternative therapies on the horizon. Still, PDT currently appears to be the best that we have to offer. As physicians, our profession is obligated to offer patients the best forms of treatment. Currently, a recommendation for therapy of subfoveal occult CNV must be accompanied by a disclosure to the patient that CMS will not cover this therapy.

The directors of AHRQ and CMS were recently quoted in the Journal of Health Affairs. They stated that failure to provide an intervention supported by compelling evidence should raise questions. So it would appear that the CMS and you panel members today must decide just how compelling the evidence regarding PDT for AMD with pure occult CNV actually is.

Although costs are not being considered in

the context of safety and effectiveness, I have the opinion that this meeting and these data would be considered to be less important if cost of PDT with verteporfin was not so high. I have been told that even the current funding situation has resulted in predicted costs for CMS of $131 million in the calendar year '02. In this context it should be noted that payment to physicians for PDT is almost inadequate to cover their costs of the drug and if the costs of the drug are allowed to increase, this form of treatment could become a money losing situation for doctors.

The entire issue of CMS payments for a variety of drugs in the same category of verteporfin needs to be reassessed. This topic is only one example of the reality that the subject of medical costs and charges versus outcome benefits is becoming an increasingly critical issue for our society. The topic of genuine practical value is of major importance to us all, but it's only beginning to emerge as a critical variable in discussions of health care and the costs of such care. So-called value based medicine is a concept in need of continued exploration.

Well, I don't see my final slide, but I

wanted to conclude that by saying that in recommending PDT for occult subfoveal CNV, we retinal specialists are hoping to provide the best care that we can, even if the practical benefit is limited. The current situation in our country does not include a mandate that practicing physicians limit their recommendations for beneficial but limited treatment based upon CMS payment rules. Thank you for the opportunity to speak.

DR. STONE: As I said, Pat gave his opinion as a practicing ophthalmologist looking at the published results, taking them at face value, but clinical trials are scientific experiments and the scientific validity of information obtained in these studies can only be properly understood after a thorough assessment of their methodologic quality. What I primarily want to talk about today was put best in a letter from Dr. Kirk Packo, president of the Vitreous Society, and Dr. Neil Bressler, study chair and principal investigator for both the TAP and VIP trials, who will both be speaking later. One must distinguish between a weak study showing a modest effect and a strong study showing a modest effect. So how strong are these studies?

Careful examination of the protocols for both the TAP and VIP studies revealed important questions, particularly in the VIP study, that must influence the interpretation of the data. These areas are prespecification of the analysis, the definition of the study population in the VIP trial, the method used for masking, the approach to missing data, the choice of primary outcome, and how to interpret the control group in the VIP trial.

These studies did not give much importance to proper prespecification of the analysis. The appropriate standards, in my judgment, are the guidelines established by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. The particular guideline that is most relevant in this case is E9, Statistical Principle for Clinical Trials. The guideline is accepted by the European Union, the FDA, and the Japanese Ministry of Health, Labor and Welfare, and is the standard for the design and conduct of clinical trials for drugs and medical devices. The ICH guideline states that for each clinical trial, all important designs of its design and conduct, and the principal features of its proposed statistical analysis should be clearly

specified in a protocol written before the trial begins.

For the TAP trial, the original protocol, including the statistical analysis plan, was approved on October 25th, 1996, and the first subject was treated six weeks later. The original protocol stated that the study results would be unmasked to the sponsor when all patients had completed their 12-month visits. The revised analysis plan confirms this and gives this date as September 25th, 1998, although the study data gives the date of the last 12-month study visit as October 3rd. A revised statistical plan was dated September 25th, 1998, but was not approved until November 24th, two years after the study began.

In the VIP trial, the original protocol and statistical plan was approved in December 1997 and the first subject was treated in March of 1998. A revised statistical analysis plan was approved the day after study data was scheduled to be unmasked to the sponsor, almost two years after approval of the initial plan. A second version of the analysis plan was approved three months after the last subject had completed two years in the study and more than one year after masking was removed and the sponsor became

aware of the results.
I don't believe, and I don't mean to imply that the first revisions in the analysis plans, although enacted after unmasking were influenced by the study results. It does appear, however, that the investigators did not fully address the statistical planning issues in both studies until the last possible minute.
Both the TAP and VIP trials were intended to be what the ICH considers confirmatory trials, intended to provide evidence firm enough to allow consideration for approval by the FDA. The guideline states that in confirmatory trials, the key hypothesis of interest follows directly from the trial's primary objective, is always predefined, and is the hypothesis that is subsequently tested when the trial is complete. The ICH guideline also emphasizes the need to distinguish the confirmatory from the exploratory aspects of the analysis.
The primary analysis of the primary variable should be clearly distinguished from supporting analyses of the primary or secondary variables. The guideline also addresses categorization, stating that the criteria for categorization should be predefined and specified in

the protocol, because knowledge of the trial results could easily bias the choice of such criteria. And here I'm referring to categorization of variables. In the TAP study the initial plan called for the primary efficacy analysis to occur at 12 months of treatment and identified two primary outcomes with two statistical analyses for each outcome. The study was divided into two separate trials. The statistical power calculations were made on the assumption of separate analyses for each of the two trials and nothing is said about pooling the results of the two trials.

This made a total of eight statistical tests for primary efficacy, but the protocol did not consider how to reconcile differences in the results of these tests. Do all eight need to be statistically significant at the 5 percent level, or just one of the eight at a much more stringent level, for example. As it turned out, if you look at the statistical appendix, only six of the eight were significant at the 5 percent level, leaving the results uninterpretable. This suggests that at the beginning of the study, the investigators were not clear about what they wanted to do.

The initial plan also placed very little

emphasis on the 24-month results, not specifying any analyses in advance, and except for the primary analysis, no analysis is described as testing any of the positives, suggesting that those analyses were intended for exploratory or diagnostic purposes. Types of subgroup analyses were listed, but divisions in these subgroups were not specified. The revised plan, two years after the start of the study, simplified the primary analysis issue but still did not consider the possibility of disparate results from the two trials. The investigators chose to focus on the loss of 15 letters of visual acuity instead of 30. Even if this choice was made before treatment assignment was unmasked, it is possible that knowledge of the number of subjects in the treatment and controlled groups combined who had a loss of 15 letters versus those who had a loss of 30 letters may have influenced the outcome, the choice of a 15-letter analysis. The revised plan was more specific about 24-month analyses, essentially specifying that the same analyses that were done at the 12 months could be done at 24 months, but that there purpose would be to confirm durability of effect. If there were no effects at 12 months, the 24-month analysis would be

unnecessary.
Here is a summary of the analyses specified in the analysis plan. One of the reasons I put this slide together was to remind us all that when we look at secondary and subsequent analyses, we are looking at a handful of analyses selected out of hundreds. I'm not talking about descriptive statistics here. These analyses refer to formal statistical tests, P values. These figures only count tests for homogeneity of results among subgroups. Looking for treatment effects within subgroups would add another 2,560 analyses. The results of analyses specified in both the initial and revised analysis plan are given in the statistical appendix.
In the initial analysis plan for the VIP trial, the primary efficacy analysis is specified at 12 months, and the primary efficacy criterion is given as loss of visual acuity of 15 letters or more. The criterion of loss of 30 letters is described as secondary but is given more prominence. It is discussed with the primary criterion and apart from other secondary outcomes.
The initial analysis plan in the VIP trial also placed little emphasis on the 24-month results,

saying, "The trial will be continued to 24 months to provide additional data on long-term safety and efficacy."

In the revised plan analysis of loss of 30 letters is no longer treated differently from other secretary outcomes. As in the other plans, they define the intention to treat and evaluable or per protocol group, with the former being the basis for the primary analysis and the other analyses are considered to be exploratory.

The initial analysis plan did not define any subgroups. It only says, "Subgroup analyses will be made to evaluate any effect of CNV lesion size, lesion components, visual acuity, and evidence of CNV in fellow eye, use of ITG, and recurrent versus new lesions." While classic and occult CNV are lesion components, there are also other components and the initial plan did not specify these as specific subgroups.

Only in the revised plan, nearly two years after the initial protocol, is there any specification of classic and occult subgroups.

Again, while there may not have been knowledge of treatment assignment, the authors of the revised plan could have been aware of different outcomes between

these or other subgroups.
The revised plan makes it very clear that any analysis of 24-month results is contingent upon positive findings at 12 months. This is in direct contradiction as to how the results of the study are presented in the published paper and by the advocates of verteporfin therapy for occult only CNV.
Here is a summary of the first two VIP analysis plans. I listed the secondary analyses in the initial plan as 1 plus 13 because of the greater emphasis given to the 30 letter visual acuity loss among secondary outcomes. The total number of analyses in the initial plan is given as more than 864 because the number of subgroups is not defined. Again, the results of analyses justified by both initial and revised analysis plans are given in the statistical appendix.
The second revised analysis plan further complicates the analysis of the classic and occult only subgroups by changing the definition of occult only to include angiograms in which classic CNV was questionable or could not be graded. This change occurred three months after the last subject completed two years of treatment, and treatment assignment had been known to the sponsor for over a

year. The second revised analysis plan clearly states that its specifications were influenced by knowledge of the 12-month results of the VIP trial. Randomized control trials are scientific experiments. At the core of the scientific method is the a priore statement of the hypothesis to be tested and the criteria which would result in the acceptance or rejection of these hypotheses. Here is the statement of hypotheses as given in the TAP protocol. As I mentioned before, the original protocol for the TAP study provided for eight different measures of the primary outcome. Six turned out to be statistically significant and we were not given the means to interpret such a mixed result. If we look beyond to the revised analytic plan, which as I said before, may have been aided by knowledge of the rates at which the 15 and 30 letter end points were being reached, only two outcome measures are given, which fortunately are in agreement and support a positive effect for verteporfin.

In the VIP trial, the alternative hypotheses were stated exactly as they were in the TAP study. According to the study protocol, the observed results require a conclusion supporting the

null hypothesis, that the proportion of patient response for visual acuity is the same for verteporfin and placebo. This conclusion has been virtually ignored in how this study has been publicly presented. Unlike the TAP study, the 12-month results were not published until the 24-month results were available. Contrary to the analysis plan, the published EIT paper made very little mention of the 12-month results and instead emphasized results in a subgroup, subjects with only occult choroidal neovascularization at 24 months, as the principal findings of the study, rather than as an exploratory examination of possible reasons for a negative result as a primary outcome. The subsequent analyses cited in papers were few among hundreds described in the initial analysis plan and were not given any special prominence in the study protocols. These analyses cannot be considered probative of the efficacy of OPT. They can only be considered to be sources of hypothesis for further clinical trials.

The secondary weakness in design that I would like to discuss is the definition of the study population in the VIP trial.

The TAP study excluded two groups of patients with AMD and CNV, the groom with occult only

and no classic CNV because the disease was assumed to progress more slowly in these patients, and those patients who had classic CNV but whose vision was so good that the risk for treatment would outweigh the potential benefit.

The VIP trial was intended to address the question of possible benefit from photodynamic therapy with verteporfin in these two distinct groups. If you think of the entire population with wet AMD as represented by the entire dark blue oval, the TAP trial looked at the group in the middle while the VIP looked at patients at both ends. Despite differences in disease characteristics and reasons for exclusion, the VIP study protocol treated these two groups as entirely homogeneous. The primary hypothesis and power calculation for the study are based on the entire population and there was no intent to stratify randomization for treatment assignment.

This approach is open to all kinds of problems. Some centers may be more able or motivated to enroll subjects with occult only CNV, others classic with good vision. The mix of the two populations in the study may not be representative of the relative numbers in the general population. The

two groups were believed to have different natural histories of disease progression. Classic was thought to progress more rapidly. Similarly, treatment effects in the two groups could be different. The TAP study showed baseline visual acuity to be an important co-variant for treatment effect and the two groups would likely vary significantly in this respect. The fact is, there was no particular interest in looking separately at the two groups through a subgroup analysis. The protocol states, "Additional subgroup analyses will be made to evaluate any effect on outcome of CNV lesion size, lesion components, visual acuity, and evidence of CNV in fellow eye, use of ITG in recurrent versus new lesions." Any attempts to recognize difference in effect between these two groups would need to rely on post hoc statistical adjustments, and given the uncertain sizes of the two subgroups, a substantial risk of inadequate statistical power. Given this problematic definition of the target population, it is unclear what a positive or negative result at the primary end point would mean.

The VIP study was not designed to look specifically at the efficacy of OPT for occult CNV in

AMD. Any analysis of such effects would be considered exploratory and not conclusive.

This third area where the two trials could have been strengthened is in how the studies attempted to mask treatment assignment. The protocols for both studies specified that the treatment assignment, placebo or active drug, be masked from patients, treating ophthalmologists, and visual acuity examiners. However, the study design required repeated disclosure of treatment assignment on site. In order to prepare treatment, the study coordinator or a designate needed to look up a subject's treatment arm every time the subject was treated, and this could be up to eight times, and follow a different process of preparation depending on treatment assignment. This process made it difficult to protect against excessive curiosity or inadvertent disclosure.

More careful consideration of the masking process could have yielded a superior alternative. There was, for example, no need for anyone at the clinical sites to be aware of treatment assignment. A form of placebo that matched verteporfin in appearance and method of preparation could have been provided.

The next area where design of the two studies could have been improved is in the approach to missing data. The analyses in both trials used the last observation carried forward approach to account for missing patient data. This method of data analysis assumes that there is no further change in vision from the time the participant was lost to follow-up. This assumption does not seem valid given the expectation of continued visual loss even with effective therapy, and could bias the results of the study in favor of the group with more dropouts. This is likely to favor the group receiving active treatment because of the greater likelihood of side effects and the lack of alternative therapies to attract away patients in the placebo group who may be dissatisfied with their results.

While it may be required for submission to regulatory agencies to do a last observation carried forward analysis for confirmatory purposes to show how much the results may have been affected by missing data, it is not necessary for it to be the primary analysis nor should it be in this context. The most conservative test is to treat subjects who are lost to the study as failures rather than successes.

In the TAP study, this did not influence the results. In the VIP study, the subject lost to follow-up are considered treatment failures, a more reasonable assumption considering the progressive nature of the disease and the apparent need for ongoing maintenance therapy, this difference between treatments in the overall group at 24 months is no longer statistically significant and the significance level for the occult group is only marginal.

There are also other approaches that require fewer assumptions and these are discussed in the statistical appendix.

The fifth area of weakness in the TAP and VIP trials is the selection of the primary outcome variable. Choice of the primary outcome should be governed by an understanding of the goal of the treatment and by whether there was a critical time or end point. Sometimes it is clear that a particular time point is more important than any other. For example, the evaluation of an intervention designed to maximize a patient's forced vital capacity before surgery would be most interested in the FVC at the time of surgery. In other cases, there may have been an important functional threshold, the most obvious being death.

This is not the case for AMD. The thresholds are not unique. The loss in visual acuity from 14 to 16 letters cannot be considered more important than a loss from 6 to 14 letters, or one from 16 to 25 letters. A treatment that led to superior visual acuity for most of the year but slight improvement at 12 months would not be considered superior if there were no assurance that the improvement would be maintained. While blindness would constitute an important functional threshold, it is the consequence of loss of vision in both eyes, not just the study eye.

In the absence of a critical time or threshold, the choice of an evaluation time point or end point threshold is relatively arbitrary and has the potential to exclude useful information and increase the likelihood of a falsely positive or negative conclusion. In these studies the primary outcome consisted of both a fixed threshold and a fixed time point.

There were better alternatives. Here are some examples. Looking at differences in numbers of letters of visual acuity loss does not require a specific threshold but does require a specific time point. Looking at the time until the threshold is

reached takes the opposite approach. Finally, is it possible to incorporate information at all time points and levels of change in visual acuity? The models described in the second part of the statistical appendix are more complex than computing the area under the curve but follow the same principle.

The final issue concerns how the control group can be interpreted in the VIP trial. As I said already, the VIP trial consisted of two types of AMD patients that have been excluded from the TAP trial. The control group allows us, of course, to see what happens to patients when they don't receive verteporfin. In this case, they begin to resemble the subjects in the TAP trial. Among AMD subjects with no classic CNV, at least 60 percent met TAP enrollment criteria during the trial. 30 of 92 developed classic CNV by month 12; 55 of 92 developed classic CNV by month 24. I say at least because we only have data on the 12 and 24-month fluorescein angiograms. Subjects could have had classic CNV on their angiograms on other visits which was no longer visible at the 12-month or 24-month visit because of bleeding, scarring, or even spontaneous resolution. Among placebo subjects in the TAP study,

the average rate of disappearance of classic CNV over a three-month period was 7.4 percent, so this clearly does happen. From this information, we estimate that subjects who began only with occult CNV presented with a history of classic CNV on approximately one-third of possible treatment visits. Again, this figure is likely to be conservative because we only considered the 12 subjects who had evidence of classic CNV at either the 12-month or 24-month visit.

Among control group subjects who initially had classic CNV with good visual acuity, 100 percent met TAP enrollment during the trial, TAP enrollment criteria during the trial. 18 of the 22 had visual acuity of 20/40 or worse at their baseline visit and the remainder had visual acuity of 20/40 or worse at their three-month visit. These subjects met the TAP eligibility requirements for 98 percent of possible treatment visits. I think what this means is that patients with classic AMD and stable good visual acuity are very rare, and that this exclusion in the TAP trial was pretty meaningless.

Given these levels of eligibility of the control group for treatment under the TAP trial, is it possible that any benefit observed in the VIP trial is the same effect observed in the TAP trial?

Is ocular photodynamic therapy with verteporfin essentially effective only for patients who have or are developing classic CNV? This would certainly seem to be the case in the VIP subgroup who began with classic CNV as they reached the TAP criteria almost immediately. For the occult only subgroup, you cannot answer this question by making separate analyses of subjects who had classic CNV noted at 12 or 24 months and those who did not.

Treatment with verteporfin removes evidence of classic CNV. In the TAP trial, among patients who initially had classic CNV, only 44 percent of treated patients had evidence of classic CNV at 24 months, while 70 percent of the subjects in the control group still had evidence of classic CNV. In the VIP study, 39 percent of actively treated patients showed evidence of classic CNV at 12 or 24 months, while this was true for 60 percent of placebo subjects. Hence, the group of actively treated subjects in the VIP trial who showed no evidence of classic CNV after 12 or 24-month fluorescein angiograms likely consisted not only of subjects who never developed classic CNV but also a substantial number of those who developed classic CNV but were successfully treated.

In the statistical appendix, you will find graphs of the loss of visual acuity broken down according to treatment assignment and whether and when classic CNV was noted. The graphs show little difference between treatment and placebo within each stratum. The principal reason for the observed overall difference between verteporfin and placebo at 24 months is the large proportion of subjects who did not show evidence development of classic CNV in the actively treated group.

In this graph of visual acuity loss among subjects who entered the trial with occult but no classic CNV, the actively treated group is represented by the dashed line and the entire placebo group is represented by the light blue line. The placebo only group is further divided into whether and when those subjects were found to have classic CNV. The yellow line shows the loss in visual acuity among placebo subjects who were not found to have classic CNV; their visual acuity was as good or slightly better than the entire active treatment group.

In other words, all of the difference between treatment arms is attributable to placebo subjects who develop classic CNV. However, it is

possible that some of the difference may have occurred in those subjects before they developed classic CNV. If so, how significant was that difference? Well, I can try to make a simple back of the envelope calculation to get an idea of what the impact would have been of treating control group subjects with classic CNV. We can estimate from the TAP trial that verteporfin treatment reduces the loss of visual acuity in classic CNV by about 32 percent. In the VIP trial, the difference between groups and loss of visual acuity among subjects who initially had occult but no classic CNV was about 6.5 letters, the treated group losing an average of 19 letters and the placebo group losing 25.5. As I said earlier, we can estimate that control group subjects who initially had occult only CNV would have had classic CNV in about a third of their study visits, so reduce the treatment effect seen in the TAP trial by two-thirds.

If we reduce the loss of visual activity in the placebo group by 11 percent to 22.7 letters, the remaining difference is no longer statistically significant. We did a more careful and complex analysis of the evidence summary but again, essentially the same result, and this estimate is

probably conservative because it assumes that no control subjects developed classic CNV other than those identified in the month 12 and month 24 angiograms, and it also assumes that the rate of visual acuity loss did not worsen after a subject developed classic CNV, which is almost certainly not the case.

In any case, it isn't possible to make a definitive statement about what would have happened if control group subjects were treated for classic CNV. I only wanted to show that it is highly plausible that it could have made a significant difference.

So even if we assume that there was a true benefit in the VIP trial of treatment over placebo, can we say that immediate treatment of all patients with occult CNV is superior to watchful waiting until classic CNV develops? Watchful waiting clearly has advantages. Fewer patients need to be treated, treated patients require fewer treatments, and this translates to fewer patients having side effects and lower costs.

So getting back to the initial question, how strong are these studies? I put together a report card summarizing my assessment in a subjective

but systematic way. I believe the VIP investigators fully failed to respect the principles behind prespecification of the analysis. The TAP has similar but less significant problems. The failure in the VIP protocol to recognize the significance of the heterogeneity of the two types of AMD patients included in the study was another major weakness. On further thought, the A I gave to the TAP study for the definition of the study population may have been a little generous, but I won't take time to go into the reasons. In both studies, the masking methods, the choice of primary outcome, and approach to missing data are very similar. In all three cases, the methods chosen were weak but acceptable. As I just finished discussing, the natural history of the control group in the VIP study leaves a positive result in that trial open to differing interpretations.

Since the purpose of my talk is to discuss problems with these studies, I did not have the opportunity to point out something that was done pretty well, the effort to make patient assessments reliable and accurate. This effort was well recognized in the ophthalmologic community and did much to create the impression that these trials were

of high quality. The overall grades at the bottom weighed these categories equally, which may be misleading. It could be argued that a trial is only as strong as its weakest aspect. If so, the TAP study would merit a C and the VIP study an F.

Getting closer to the questions that the panel is considering today, does the VIP trial show ocular photodynamic therapy to be effective in occult CNV? This trial had a negative principal result, supporting the null hypothesis of no effect. You cannot use this study to make the opposite conclusion. The VIP study was not designed to answer this question. The study population was a mixture of occult and classic patients. There were other methodological weaknesses concerning choice of outcome measures, masking procedures, and treatment of missing data. Exploratory, secondary and subgroup analyses give varying results, some positive, some negative, some marginal. It is not clear that any effect that may exist is not equivalent to the treatment of early classic choroidal neovascularization.

Finally, I should point out that there was a 5 percent rate of significant severe side effects, primarily acute loss of vision.

I know this has been long and complex presentation. Thank you for your attention.

DR. DAVIS: Thank you very much to you and your co-presenters. We are I guess about 15 minutes behind schedule, we will see if we can make that up during other portions of the agenda, perhaps open public comments, depending on how many of those we have. And I hate to suggest this, but maybe even during lunch. But why don't we proceed without further delay with the requestor's presentation.

DR. RAAB: I have one question before we go on.

DR. DAVIS: You know, we have a specific part of the agenda that refers to questions to presenters at 11:20, which will probably come a little bit later. I wonder if you'd be willing to hold that.

DR. RAAB: It's a clarification from CMS if possible.

DR. DAVIS: On the content of their presentation?

DR. RAAB: Yes.

DR. DAVIS: Would you be willing to hold it in fairness to the requestors?

DR. RAAB: Sure.

DR. DAVIS: Why don't we proceed now with the presentation by the requestors, Dr. Neil Bressler and others as listed on the agenda. We have a scheduled break after that, but obviously, if members of the committee need to get up to use the restroom or for any other purpose, they can do so.

DR. AZAB: Mr. Chairman, ladies and gentlemen, members of the panel, while he is setting up our presentation because we will be running from this laptop here, my name is Mohammad Azab. I am the chief medical officer of QLT, the manufacturer of verteporfin. I am honored to be here with you today. I have more than 20 years of clinical research experience during which I supervised global drug development for seven new pharmaceutical and chemical entities that are currently on the market.

I have been involved in the verteporfin clinical research for more than six years, since the start of the TAP trials, and in addition to my medical and oncologic training, I also have a degree of statistics and applied statistics in clinical research. I will be happy to provide here any clarification that would help the committee to decide on the questions that they have in front of them today, and for that we have a presentation today and

the agenda of which will start with Dr. Bressler. Dr. Bressler is professor of ophthalmology at Johns Hopkins. Because of his extensive clinical experience in age-related macular degeneration, he was the chair of the study advisory group that supervised the design and the conduct of the TAP and the VIP trials.

In addition to Dr. Bressler, I will follow that with a presentation to address the specific issues that were raised by the CMS in their presentation and analysis that was submitted to you. Following that, Dr. Kirk Packo will be presenting on behalf of the American Society of Retinal Specialists, and then Dr. George Williams will be presenting on behalf of the American Academy of Ophthalmology. We're glad to have Mr. Charlie Crawford with us today, who is the head of the American Council of the Blind. And we are extremely grateful for Mrs. Lois Jalbert, whose altruistic challenge to the coverage decision of the CMS has brought us here today. She will be presenting on behalf of the patients suffering from this disease.

We're also glad to have two guests available for questions from the panel in their capacity, Dr. John Paul in his capacity as the

current chairman of the data and safety monitoring committee that supervised these trials, and Dr. John Paul is a professor and chair of ophthalmology at Northwestern. Professor David Andrews is the former chairman of the department of statistics of the University of Toronto. He has done an independent statistical analysis of the data. Both Professor Paul and Professor Andrews have had access to the raw data and done their independent analysis that concluded that the treatment was effective, there is evidence of efficacy in the occult CNV, and they will be happy to share their conclusions and their rationale with you today and answer any questions. Without any further ado, I will ask Dr. Bressler to start with the overview of the data.

DR. BRESSLER: Thank you. Thank you for allowing me to have the time to share this all with you. My name is Neil Bressler, I am a professor of ophthalmology at Johns Hopkins and am an ophthalmologist there and retinal specialist. I probably treat hundreds if not thousands of people with macular degeneration over the years and I also in my time like to spend time helping to design and work on clinical trials, mainly in macular degeneration because it is such a huge public health

impact in the United States and the rest of the world. I am study chair for several randomized clinical trials sponsored by the National Eye Institute, the National Institutes of Health, and that's how I got involved in working on trials sponsored by industry as well. I also serve a editor for one of the lead ophthalmology journals, the Archives of Ophthalmology in one of their controversy sections, and so I think that's appropriate to where we are today. I serve also as the chair of the data monitoring committee for the National Eye Institute's intramural clinical trial programs.

I come to you during the presenter's time as the chair of the study advisory group, which is serving sort of as the study chair for the clinical trials, and I would like to walk you through the history of how we got to where we are today and give you our understanding of the results. Dr. Azab will address some of the critiques that were brought up by CMS just previously. I have no direct financial interest and no direct financial compensation from any of the companies for this. I did receive financial compensation through 2002 for consulting for the companies for this, but no longer, and those were managed by the Johns Hopkins University conflict

of interest committee. My department, though, does still receive funds for research and for efforts that we do in these trials, from Novartis and QLT. Pat Wilkinson gave a nice overview of what macular degeneration is, and I only want to highlight some items that are critical to the parts that I will be discussing. This again, is a diagram of a normal retina that we're looking at, and looking in cross-section. The color of this retina is from the pigment and the pigment epithelium. It has a very thin basement membrane that separates it from these blood vessels in the choroid. Unfortunately, people can get an abnormal thickening to this basement membrane, and it happens to probably about 200,000 people each year in the United States. The ingrowth of blood vessels and scar tissue can grow into this area and unfortunately, these blood vessels and scar tissue destroy the photo receptors and the pigment epithelium, the rosin cones that we use to see. And so this scar, which can take sometimes three months, sometimes three years, maybe never develop, it's a very variable outcome, but it leads to what is the leading cause of blindness in people over the age of 55 in the United States.

As was mentioned, this is a particular

problem when it affects not only your first eye, but also by the time it affects your second eye, you will have difficulty reading, telling time. You have difficulty being social because you no longer can recognize people's faces. You of course cannot drive when this affects both eyes.

This is some information from the NIH sponsored submacular surgery trials. It's looking at where people place their preference value. This was directed by Eric Fass at Johns Hopkins. When you have subfoveal choroidal neovascularization, among 792 individuals that were participating in one of our trials, where zero is death and 100 is perfect health. You can see that people value this condition at about 64, which is somewhat less than the literature states for congestive heart failure. It's about equivalent to where people value symptomatic AIDS. Here you can see minor stroke also, as similar to having the impact of subfoveal neovascularization. It's a little higher than where we put chronic renal failure on home dialysis, but in the subset of people here that had neovascularization in their second eye it was at about this level, where people put chronic renal failure on home dialysis. Complete blindness, somebody's state of health would be somewhere in the

30 to 40 range. This means that even relatively expensive treatments probably would be cost effective from the patient's point of view because they put such a low value on preferring to have this condition. As was mentioned earlier, when somebody walks in with this neovascularization, we obtain a fluorescein angiogram. We first look at the location of the neovascularization. Rarely, it does not involve the center of the retina. Here's some fluorescence of neovascularization, here's the center of the retina, here's some fluorescence right next to the center. We apply laser photocoagulation in these cases. Unfortunately, only 5 or 10 percent of the cases don't involve the center, about 90 percent involve the center, as in this case, where laser would be usually more destructive, unless it was very very tiny when it walks in. So that was the rationale behind trying verteporfin therapy, which was less destructive than laser. The drug is infused over ten minutes. It fortuitously concentrates in this abnormal blood vessel and scar tissue developing in the retina. When we apply a light through the eye transparently, the light activates that neovascularization to try to

selectively damage the neovascularization and not affect the retina tissue, which is almost like brain tissue, that we're trying to preserve whatever still works there.

So when we designed the TAP investigation, why did we start with classic containing lesions? Data from the macular photocoagulation study sponsored by the NIH that I helped to work in as a leader showed that lesions with classic neovascularization were more likely to deteriorate in a short time period without treatment, and so we planned at the onset to do subject analyses based on the data that we were collecting in a photograph reading center at Hopkins to analyze the angiograms for features that might be suggested from previous trials to affect the outcomes. This included the size of the lesion, data on the initial visual acuity from the clinical centers, and data from looking at the angiograms of the amount of classic neovascularization, the amount of this that would be seen fluorescently. That will tell us what the lesion composition was.

The follow-up was excellent in these trials given the fact that the average age of these people was 75, and someone had to walk in with them

to assist. Many of them had to come in at difficult times when they might have perhaps a conflict to come in for a three-month follow-up plus or minus two weeks. Despite that, we had about 94 percent come in for the month 12 exam and 84 percent come in for the month 24 exam. This includes, unfortunately, people that are going to pass away in this age group. This rate of follow-up was as good or better than any of our trials in macular degeneration. You would suspect that people were assigned to placebo and continued to lose vision would perhaps say I'm doing terribly, why should I still come in and yet, we don't see a difference in the return rates for the placebo or the verteporfin group.

We also did significant training of all the people involved to try and maintain masking. This shows you over time on the X axis, 0, 12, 21 months, whether or not the person received their assigned treatment. They could have been assigned at baseline to verteporfin or placebo, and what this slide slows is that people did not get treated at every visit. At the initial visit, 100 percent were treated as assigned. As we look over follow-up, fewer and fewer people were receiving treatment with both verteporfin and placebo, because treatment was

only given when we saw fluorescein leaking on the angiogram at follow-up from neovascularization. This was chosen because we suspected that that was a sign that the lesions were likely to grow. And certainly in the Phase I and II trials that led to this design, when cases were treated and leakage returned, if it was watched, it continued to grow. So we're trying to stem the growth until there was no longer any leakage.

In our clinical practice, we probably treat much less than this. This averaged to about four to five treatments over two years. In published papers from clinical practices applying this now, they apply an average of maybe two to three treatments over two years. This is because we know that the person is getting a treatment, and so when somebody comes in at perhaps month nine and we see some questionable leakage in the trial, we didn't know if they were getting treatment or placebo, we didn't know if the treatment worked. We pushed the people to be treated, saying any leakage, treat. In our practice, if we see somebody with leakage, if it's suspicious, we have the luxury of saying why don't you come back in a month, let me make sure this is really leaking and if so, then apply the treatment

and if not, continue careful watching. And that may explain why the fact is that we do far fewer treatments, which of course is good for all of us in society because it means it actually costs less than an average of four to five treatments that was predicted from the trial.
This was the primary outcome in the TAP investigation. As ophthalmologists, we always report that people that lost at least 15 letters, that is moderate vision loss, that had a 15 percent difference at one and two years, rather than this responder rate, which is the way the regulatory authorities have collected the information. In any event, you are less likely to have a loss of at least three lines of vision.
The same was true for loss of at least six lines of vision. This was looked at because this was the main outcome in the macular photocoagulation studies where we were looking at outcomes for choroidal neovascularization in trials sponsored by the NIH in the 1980s and early 1990s. This was what we thought was a severe amount of vision loss.
Again, it was less likely in the verteporfin than in the placebo group.
Now, are these adequate reflections of

vision outcome? We think so. In a recently published article in the March 2003 Archives of Ophthalmology, we looked at the responsiveness of the National Eye Institute visual function questionnaire, to visual acuity, where we showed in the submacular surgery trials among hundreds of patients that have subfoveal neovascularization in AMD, a three-line change in visual acuity, which we were calling at least moderate vision loss, translated to an average seven-point change in the overall NEI visual function questionnaire. A six-line change, that ophthalmologists thought was a significant outcome for people, translated to a 14 point change. And vision function experts consider that a five point loss is a significant worsening in function. So we think what the ophthalmologists believed was confirmed subsequently when we had instruments to measure visual function as a reflection of our visual acuity.

We got into a more complex discussion then when we looked at the TAP investigation, and we had planned at the onset to look at what were the outcomes if the person had predominantly classic neovascularization, of there was only a little classic neovascularization, what we called minimum

classic, or there was no classic neovascularization. This was that primary analysis in that planned subgroup, where we can see that for the predominantly classic cases, the risk of at least moderate vision loss was estimated at 41 percent compared to a placebo at 69 percent, but for the minimally classic lesions, we saw no difference.

Now, there were 61 out of 600 cases that had no classic neovascularization and again, we saw a difference in favor of verteporfin but this was a small group, we hadn't planned to enroll these, this is based on an analysis at a central photograph reading center, not the clinicians' judgment. The clinicians all thought these were classic containing lesions. So ignoring this, we see that maybe we should just recommend verteporfin for predominantly classic lesions, and that's where we were.

Many of these, as Dr. Wilkinson pointed out, have occult neovascularization, most of them do, but we were recommending that predominantly classic lesions receive verteporfin therapy with or without occult neovascularization, or at least be considered for treatment, and that's where we were.

Now while the TAP investigation was going on, at a point when it seemed that there were no

obvious safety problems, even though we were masked to the results, we decided also because of the huge public health impact of this problem, to pursue this treatment in macular degeneration lesions that were not intact but likely to deteriorate. So this was already explained as those classic lesions with excellent vision that we now are willing to take a chance, even though their visual acuity was excellent, better than 20/40, but also occult with no classic neovascularization, but I want to point out a very specific subgroup of the universe of occult with no classic neovascularization. These people had 20/100 or better vision, even though in TAP it was 20/40 to 20/200, and these people all had what we call presumed recent disease progression. We all had experience of occult with no classic lesions that remained stable for years at 20/40 or 20/50 or 20/80. We only wanted to enroll patients that we thought were likely to progress. So this was the subgroup of occult with no classic that was out there in the clinics that either had blood or had deteriorated by at least a line of vision in the last three months, or had grown on angiography by 10 percent within the last three months.

The follow-up, again, was excellent

considering the age group, which again, was an average of 75. We have about 91 to 93 percent by one year, and about 86 to 87 percent by two years. Again, I don't suspect there was any unmasking, given the follow-up being very similar in the placebo and verteporfin group.

Now this is why we're here today, the outcome that had been chosen almost arbitrarily at one year to be a three-line loss was only a 3.7 percent difference for all the AMD patients in the VIP trial. This is both those classic containing with excellent vision and the occult with no classic. We always had planned to follow out to two years, as recommended by the data monitoring committee at the onset of the trial, and in all of our trials we think you need at least two years of follow-up for AMD outcomes with neovascularization, and this was 13 percent. And so looking at all this information, it was suggested to us that there was a benefit.

Now we had planned at the onset to look at the occult with no classic neovascular lesions. This was about 75 percent of the entire AMD population that was in the VIP trial. These results are similar because it was driven by 75 percent of the cases where again, no obvious difference for at least

moderate vision loss at one year, but a difference that was a modest effect by two years. But looking at all other outcomes that are typical, that we always do in all of our trials with neovascular AMD regardless of the treatment modality being done, and that we had planned in this trial as well, the average visual acuity loss showed 15 letter, which is equivalent to about a three-line loss with treatment at one year, compared to 20 letters or four-line loss for the placebo group. Again, because the primary outcome that was chosen as three-line loss at one year was not significant, we looked at this with interest but we waited until we had all the data out through two years, which again maintained this difference in the verteporfin versus the placebo group. Those that were less than 20/200, which when in your second eye, meets the criteria of legal blindness if your first eye has already lost significant vision, again were in favor of the verteporfin group.

We had looked again at parameters that we thought might influence the outcome, not the lesion composition now, because we already were looking within the occult with no classic lesion composition, but other outcomes that we knew from previous trials

might affect the outcome. This included the initial visual acuity and the lesion size. And looking at the lesion size here, because I think this helps explain the disconnect of the predominantly classic and occult with no classic appearing to work, and the minimally classic not working, when we look at the baseline lesion size within the occult with no classic group, we see for the smaller lesions there was a difference here for verteporfin compared with placebo, but not necessarily for the larger lesions looking at three-line loss. And this is for six-line loss, where again, for the smaller lesions the more obvious effect, 20 percent with severe vision loss estimated compared with 50 percent, and only a small difference here for severe vision loss in favor of verteporfin for the larger lesions.

Again, as was mentioned in the VIP trial, we saw that acute severe vision decrease, that is, a loss of vision within a week after treatment of significance that we said was four lines or more, happened in 4 percent. Now some of these recovered by three months, so it was down to 2 percent by the time we got to three months and already the natural history had caused at least 2 percent losing severe vision loss, but this was important to know for

people who are receiving this therapy. The other side effects were not judged to be very clinically relevant for the patients.

So that we concluded in 2001, again, our initial conclusion, consider photodynamic therapy for predominantly classic lesions with or without occult neovascularization, and now consider it for occult with no classic but not any, those with presumed recent disease progression. And we cautioned our ophthalmologists to consider it, perhaps especially if it's relatively small, or maybe only if the visual acuity was already significantly deteriorated, and now warn all patients receiving the therapy that there is this risk of acute severe vision decrease but this appears to be outweighed by the treatment benefit that reduced the risk of severe vision loss over time.

So now the disconnect. Why is this beneficial for predominantly classic and occult with no classic, but not minimally classic? I don't think it's for all the hypothetical reasons presented just a few minutes ago, I think it has to do with the lesion size. If we look specifically in retrospect, once we saw this disconnect, we had only looked at an effect of the occult with no classic where we saw

that there was a benefit for the smaller ones rather than the larger ones. We had looked at lesion size for the TAP investigation but only for the entire TAP investigation, all the classic containing lesions. We had not looked at lesion size within predominantly classic or minimally classic. So now we go back and look at that and we see that the predominantly classic lesions were smaller at baseline, even though they had the worst visual acuity at baseline. So in an article that is just published this month in the September 2003 American Journal of Ophthalmology, we show this information that indicates using a multiple linear regression analysis, we are trying to control for these factors that we think affect the outcome like the lesion composition or the baseline line lesion size, or the baseline visual acuity. When we control for those in the occult with no classic lesions, there is a treatment benefit interaction depending on the lesion size. The same is true for the minimally classic lesions, not necessarily as strong for the predominantly classic. The baseline visual acuity, though, does not appear when controlling for baseline

lesion size to have an impact on the treatment benefit for occult with no classic, minimally classic or predominantly classic.

When we put all the cases together from TAP and VIP and we see, is there an interaction of the lesion size on the treatment benefit looking at all the lesion compositions and controlling for that in the model, we see that there is an interaction of the lesion size to the treatment benefit, not so strong for the lesion composition, and not at all for the baseline visual acuity.

Taking this model, this shows for the predominantly classic lesions in TAP at very small lesions, one disk area on the X axis, three disk areas, six disk areas, nine disk areas, that always there is an average visual acuity lost from baseline to two years for the verteporfin group but it was always less than the placebo group. So we suspect that no matter what the size, the predominantly classic lesion is going to have a much worse outcome without treatment than with treatment. But for the minimally classic, we hadn't looked among lesion sizes, and looking from this model that we describe we can see that at the smaller lesion sizes, the average visual acuity loss from baseline to two years

is less in the verteporfin group than in the placebo group, not as we get to these larger sizes. And the same was already known, then, from the occult with no classic, from the planned analysis of the lesion size within the occult with no classic lesions, where again, at the smaller lesion sizes the average visual acuity change at each of the smaller lesions was less than for the placebo group. Now we did based on this information put together a small trial called the VIM trial, which looked at subfoveal neovascularization in minimally classic lesions, but we said let's just look at smaller minimally classic lesions, not the ones that were enrolled in TAP. This is just the top line information from that which is being submitted for publication. At the one-year outcome, looking at a very small group, just 40 placebo, this was just to explore, a larger randomized trial is now being planned based on this that we just had a meeting for this weekend, looking at the placebo group her of just 40, compared to either reduced fluence of verteporfin or a standard fluence, that depends on how much light dose we are giving, we have 18 out of 40 with a three-line loss with placebo, 7 out of 38, 18 percent with this reduced light dose, and 10 out

of 39 with a standard light dose that was used in TAP. So again it appears that as we concentrate on smaller lesions, maybe these minimally classic lesions would have worked, and although the overall results of TAP was classic containing lesions had a benefit, I think we were appropriate in being conservative and starting just with predominantly classic lesions, but I think we have a better understanding now as to why we had this disconnect. Maybe lesion size data explains the inconsistency and maybe we should be concentrating on trying to consider treating occult with no classic but when they are relatively small.

So occult with no classic lesions, we have concluded do have a treatment benefit when they're relatively small. Among the minimally classic lesions in TAP we didn't see a benefit, but an exploratory analysis suggested a benefit when they are relatively small. Lesion size data is consistent with what we saw in the occult with no classic lesions, and the VIM trial has confirmed this benefit in a small randomized clinical trial.

So where are we in 2003? We recommend predominantly classic lesions from 1999; the occult with no classic, especially if they are relatively

small; and we need to determine further to try and help these people with whatever treatments we can come up with, and I hope that there are better ones and I hope there are less expensive ones over the next decade. But we need to figure out if there is a way to reduce the impact of the vision loss.
So, is there adequate evidence to draw conclusions? Our conclusion would be yes. Looking at the entire universe of information out there, not just the isolated VIP trial but all the information from TAP and the VIP trial, it was a randomized double-masked placebo controlled. It was analyzed as intent to treat. The baseline features were similar with respect to known prognostic factors.
Approximately 75 percent of those enrolled in the VIP trial were occult with no classic. There was no unmasking known during the trial by patients, clinicians, those that were assessing the outcomes, the visual acuity and the photograph graders. The follow-up was as complete as me might expect in this disease. There were multiple outcome assessments that show a consistent result for what we were looking for.
So is this evidence, then, improving the net health outcome in our patients with macular

degeneration? It's the lesser of two evils. I wish we had something better. However, it does reduce the risk of at least moderate visual acuity loss at two years. It was a 20 percent difference with a 95 percent confidence interval between 2 and 38 percent, and looking at severe visual acuity loss, an important outcome, always a planned outcome, fr the occult with no classic there was a 38 percent difference with a 95 percent confidence interval of 12 to 64 percent. This is consistent with the TAP investigation and the VIM trial when we take into account both lesion composition that causes a whole morass for all of us in analyzing this, and when we take into account lesion size. This does appear to translate into a visual function benefit for our patients and I hope you will consider helping these patients in being able to afford this therapy until we come up with something better, if a physician concludes that they want to consider it.
Thank you very much.
DR. AZAB: Thank you, Dr. Bressler. Mr. Chairman, ladies and gentlemen, I would like to say that, to draw your attention that we had to make several changes to the presentation that we submitted to you on August 21st. At the time of our submission

the CMS did not share with us that they have many of the methodological issues that they have presented to you today. That's why we feel that we need to present more of the data and its interpretation today. We felt obliged that we need to address the methodological issues that were presented to you by the CMS analysis. So I am extremely grateful if you'd bear with me with some of the new slides. Because of the CMS procedures, we were not allowed to hand out any new prints for you, but the new slides will be shown here and if you see any of the new slides, it will be shown up on the screen. So I appreciate your patience for this.

What I would like to run through here is quickly and briefly the mechanism of action in terms of verteporfin on the classic and occult patterns of CNV, which merely are just to angiographic patterns of really the same disease. I would like to go through an overview of the evidence, the totality of the evidence from the VIP trial, and I would like to emphasize that all I'm going to show you today were prespecified in the original protocol and the original analysis plan, and we have copies of those available if there are any questions or clarifications. I would like to address all the

misconceptions and the other issues from the CMS analysis. I will give a summary and a brief report about the regulatory status of this drug in this indication, and the expert and scientific community support that we have. Finally, I hope to conclude with what would help you in the decision today.
What I would like to show here is just how does this therapy work. This is a classic representation of a mixed lesion. Usually these angiographic patterns of leakage actually are presented in the same lesion, they coexist in the same lesion. So this is a typical mixed lesion that are mainly composed of a classic component here and there is an occult component here. This is before treatment.
One week after treatment, what verteporfin essentially does, it closes the abnormal blood vessels and results in cessation of leakage. And as you can see here, the area corresponding to the closure of the blood vessel, which is the dark central area, actually encompasses both the classic and the occult components.
So at the outset, you are not really expecting that, because it's the same disease, it's just two angiographic patterns on leakage, that there

will be any difference in the cessation of leakage with classic and occult patterns with verteporfin therapy.

There is really nowhere in the CMS analysis that you are able to see the totality of the evidence and we believe this is really what we are here to do, is the totality of the evidence of effectiveness from the occult disease in the CNV VIP trial. This also presents the data, by the way, when Dr. Mosier has the benefit of hindsight, of actually looking at the data after two years, but here, this is how we got the data first at 12 months, how it looked like, and what was our decision, and then at 24 months I will show you the data.

All these data are prespecified efficacy variables. We did say we had one primary efficacy variables outcome in the 12-month analysis, which was a three-line loss or the moderate vision loss, which is the first line, and that's probably the reason we're here is that, as you see, if you look just at this line in isolation of all the other prespecified evidence, then you will see that this did not achieve a statistical significance at primary analysis time point of the 12 months.

But if you look at the totality of the

evidence from the top half, which is the visual acuity variables that were specified in the protocol, three-line loss is presented here as a moderate vision loss, this is the severe vision loss or the six-line loss of patients, which of course is a much more severe outcome for the patient. This is the visual acuity stage of less than 20/200; this is the level of legal blindness. So, a threshold of less than 20/200 is a clinically relevant threshold for the patient. And then the average visual acuity score, which looks at all the visual acuity scores for all the patients. All these are very relevant visual acuity outcomes.

You can see we have some preliminary evidence of efficacy in almost all of them already at the 12-month analysis, but they were not the specified primary efficacy variables. There was some evidence of the contrast sensitivity but weak at 12 months, and there are strong evidence from all the angiographic variables, this is the biological effect of verteporfin. It stops the progression of classic, it stops the progression of occult disease, at significant P values. It stops the conversion to classic. So actually when you give it to a patient who is classic, it stops the conversion to classic.

And as you heard from Dr. Bressler, this is already a benefit to the patient, because the classic lesions are in the consensus of the expert community, this is an aggressive lesion. So, it stops the conversion to classic at a significant level and stops the growth of the lesions. The lesions who are large are significantly less on the verteporfin arm, and at that significant value, already at 12 months. Of course when we saw this data, it was irresponsible for us to say we did not see a primary efficacy variable effect that we have prespecified, we will ignore all the other efficacy so we will just stop there. So it was very logical, and it was a unanimous recommendation from the study authors and the DSNC that we have to continue the trial to its full duration. The duration of the trial was 24 months. And we're going to repeat all these variables, we're not going to dig up any new variables, we will repeat all these variables at 24 months to see how it pans out.

This is how it looked like at 24 months. As you can see here, almost without exception, the totality of the evidence, once again, all prespecified efficacy variables in the original protocol and the original analysis plan that had, you

see at the difference column or at the P value, highly significant variables between the visual acuity scores, the contrast in sensitivity, both of which are indicators of the visual function of the patients, and the angiographic results which also indicate how does this therapy work. So all the data made sense in terms of looking at the totality of the evidence, not just at the one primary outcome at the one primary analysis point at the 12-month time point.

I would like now to go through the methodological issues that Dr. Stone went over from the CMS analysis, and there are many of the new slides in this part of the presentation.

The main methodological issues that were presented, we believe that there are misconceptions or some misunderstanding of some reading of the protocol and confusion between what's the purpose of the protocol and the analysis plan, and also the masking method, I think there is some data that were missed in terms of how did we get to that masking method. I will go also through the study population, the choice of the primary outcome, the size and duration of benefits, the approach we used for missing data and explain why we did that, the

interpretation of controls, and also of course the safety, because in order to evaluate the benefit risk we have to go through the only really clinical issue we have, which is the incidence of the visual acuity decrease at 45 percent.

Now, as I said, it was a surprise to us that there were a lot of methodological issues raised with you today about the trials. This is what the CMS coverage memorandum of October 17, 2001 said about the VIP trial, which really summarized the totality of the evidence that I explained to you in the previous slides. The VIP study was well designed with limited potential for unintentional bias. It was a double masked placebo controlled randomized, and included evidence from 28 centers across North America and Europe.

There were consistent results across two vision outcome assessments. These are the visual acuity assessments and the contrast sensitivity, as well as confirmatory fluorescein angiographic studies. The authors also reported consistent results across all study centers. Given these consistencies, the treatment benefits seen with verteporfin seems unlikely to be due to chance.

It is true after this coverage memorandum,

the CMS decided to reconsider the evidence, so between October 2001 and March 2002, we gave them all the raw data that they asked for, we gave them all the analysis that they asked for, and at this time we had an independent statistical consultation for the interpretation of the data and yet, after the interpretation of the data and citing many issues that we have with the data and their interpretation, they still concluded in March that the VIP study was well designed, double masked, placebo controlled randomized trial.

Having said that, we are glad to be provided the opportunity to clarify any misconceptions about the methodology of this trial.

The first methodological issue, that the analyses were not prespecified, I would like to clarify to you that all the primary and secondary efficacy variables that I'm giving to you today were described in the original protocol back in '97 and also, the detailed analysis of these variables were described in the original analysis plan in October '99, and I will show you that all these decisions and variables were fully described before any unmasking of the data.

The other misconception that there were

hundreds of analyses, and this is really counting detailed analysis plan of hundreds of data points that we have in the registration study, this was a huge registration study and there were hundreds of data points not related to the efficacy necessary and safety. The fact is, I would like to clarify also, that of these hundreds of analyses, what really matters is what I showed you from the data about the efficacy. There was one primary efficacy variable and nine secondary efficacy variables, and all these variables included also analysis of one primary data set.

The conclusion of the trial came, by the way, not from the occult subgroup analysis. It came from the intent to treat primary data set analysis, and I will show you these results. These primary data set of the intent to treat patients were actually stronger than the occult subgroup, as I will show you later.

The other misconception was that the analysis plan was revised several times. There is a confusion in the CMS analysis between two separate documents, the protocol and the analysis plan. There is a confusion that the analysis plan is actually a revision of the original statistical section of the

protocol. That's not true. The analysis plan says exactly the same thing as the protocol but with much more detail, that is actually what is in the ICH guidelines, and the analysis plan is always written after the protocol or before the unmasking.

The other misconception is that the trials were unmasked the day of the last patient visit. That was the assumption from the CMS. Actually, all our analyses were finalized before any unmasking. The unmasking was done after all the data from these patients were in house, clean, QA, and the database closed, and the unmasking occurred four months after the last patient visit.

The analysis plan was written two years after the trial start. Well, the trial took three years, there was one year enrollment and two years follow-up, so the most important point here to make is that the analysis plans were finalized at the end of the trial before any unmasking. That's not unusual and actually described in the ICH guidelines under the description of the statistical analysis plan.

The definition of occult change, that only affected the small number of patients in who the central reading center was not able to provide a

grid, for exactly 24 patients. As a matter of fact, when we do the analysis of the occult subgroup with the original definitions, the results look stronger, so the revision of the definition was at the request of the investigators, in order to be able to assign a grade to the patients since they were not being graded by the reading center, it was questionable and they cannot grade category, that we have reassigned. And if you look at the poor occult lesions analyzed by the reading center and confirmed by the reading center as occult, we lose 24 patients from the analysis but the analysis becomes stronger, with more statistical significant P value, lower P value, so we did not do that to make the results look better, actually. It didn't work for our advantage. The 24-month analysis was not specified. There were specific description, small in the protocol, but in the analysis plan there was a full description of what we were going to do at 24 months. That is fully described in the section under schedule of analysis. This is the prespecification of analysis criteria, and the ICH describes two documents that actually talk about the prespecification of analysis. On is the protocol, which I believe Dr. Stone gave

you, but really the protocol is a document in which the statistical section is a more high level section in which the important details of the design and conduct and the principal features of the statistical analysis will be described. The VIP protocol complied with all of that.

The second is the statistical analysis plan that is often referred to you in the CMS analysis as a revised plan. It is not a revised plan, it's simply a detailed description of the analysis that is exactly identical to what we said we were going to do in the protocol, but simply more details. That is not a revision, that's the original analysis plan.

And the most important part in the determination of prespecification is that the former records should be kept when the statistical analysis plan was finalized as well as when the blind was subsequently broken. The VIP original analysis plan in October complied with all of that.

These are the correct dates that we have to prove the prespecification of the analysis in terms of primary and secondary outcomes. As you can see here, the most important dates are the dates of the original statistical analysis plan finalized,

that was October, 1999, and the database close and the statistical unmasking starting was in March, more than four months after the finalization of the analysis plan. Everything that I described to you today follows the protocol and original analysis plan, and was prespecified. In the CMS document, they made the assumption that the unmasking occurred on October 18th, which is incorrect.

Now they also talk about the masking method and ideally, yes, you ideally want to provide a matching placebo so that nobody in the center is unmasked, but we could do that practically for verteporfin because verteporfin is a very dark green powder and when you reconstitute it in solution, which must be done at the center immediately before injection, it becomes a very dark green color. There is no dark green dye that we can safely give to humans that when reconstituted will give you a dark green colored solution, so basically we cannot do that. So once we had decided that we cannot do that, and actually we did prepare a fake cake of verteporfin, and of course you can see that it cannot be used as a matching placebo. We did decide that there would be one person at the center that will be unmasked, but of course we did set according to

standard practice very rigorous rules and procedures to make sure that that unmasked person who had access to the code in order to prepare the infusion and give it to the patients is completely dissociated from any analysis or any assessment.

As you can see here, the assessment, only a study coordinator or a designee will be unmasked. The investigator will do the eye exam and the safety assessments. The vision examiner, a certified vision examiner will do the vision outcome assessments. The patient is unmasked. The angiographic assessments were done by a photographer and were not even read by the investigators. They were sent to a central reading center; from all over the world, the Wilmer reading center reads the angiographic assessments, so they actually were completely separated physically from the patient and where the picture was taken.

The potential of unmasking affecting all these assessments simultaneously is extremely remote.

In addition to that, we have conducted several -- the monitors followed the procedures, closely monitored the centers, and we have conducted severing audits, and we did not discover any irregularity in unmasking.

What was surprising to us, once again in

the raising of all these issues, the masking of VIP and TAP studies were completely identical. We have disclosed almost in a half a page of the first publication of TAP four years ago and all this was available to the CMS, all the masking procedures and the reasons why we had to do that, explaining the color of verteporfin and everything. All this was available for CMS for their analysis.

Now I would like to assess the other issue in terms of the occult analysis was not a prespecified subgroup in the original protocol. Well, in the original protocol we only described that we would do different subgroups including lesion types, and it is true we did not define a separate full analysis section of the occult population. But that was for an obvious reason and the reason for that is that the protocol was written in December '97, and the TAP results that showed the treatment interaction with the lesion type was only available in December '98, one year after we wrote the protocol. So it's true that we included these two types of patients in the protocol. At that time we felt it could be homogeneous patients, not necessarily heterogeneous, because as I told you, the verteporfin worked for both components in the Phase I

and II studies angiographically.
So when we found the TAP results, it was very clear and the DSMC made a formal recommendation in the minutes recorded, and we have that in house, that the VIP analysis plan should consist of a separate analysis of the patients with occult only lesions at baseline. That was in August of '99. Of course we took up that recommendation from the DSMC and we applied it to the original analysis plan that we had finalized in '99, more than four months after any unmasking of the patients. So that decision about the separate analysis of the occult was prespecified and we had a complete section in the analysis plan about this. The analysis plans of the protocols were provided to CMS for their consideration.
The other important point that I would like to raise about the occult subgroup is a lot of things have been mentioned, and we're talking about occult because it makes sense as a group to cover from the VIP trial, and it is the largest group treated in the VIP trial, but I would be very happy to cover anybody included in VIP based on the intent to treat analysis. We just made the decision that the coverage makes sense, of course from the

investigator's perspective, from the DSMC, from our perspective, this is the largest group that drives the results, this is what the study authors recommended to do.

But the VIP intent to treat analysis, which is the primary data set, the prespecified single primary data set, had exactly the same results of the occult with no classic. If you look at month 12, there is some evidence of it, and I'm only showing here the visual acuity results, I'm not showing the contrast in safety and angiographic, which almost look exactly the same, but the visual acuity results as you see from the difference columns and from the P values, was almost identical to the occult group. That's not unexpected because the occult group was the largest patients in this trial. And if you look at month 24, actually the intent to treat data are stronger. If you look at the difference, the difference is the same, but if you look at the P values, because of course this is the entire study group, you have more patients, the P values are actually showing lower P values and more significance. So we're not trying to salvage a negative study by trying to look at a subgroup that showed benefit while the intent to treat primary data

set failed.
We believe that this is the issue that really the committee is here for today, is the choice of the primary outcome. We did make and we fully acknowledge we did make a mistake. We did not know at the time all the natural history of verteporfin effect on treatment and we didn't know that the deterioration of patients could differ between one year and two year, and would did make a mistake of choosing the primary outcome analysis at one year. Yes, we fully admit that, that's why we are here today, and if we had the results at 12 months, we wouldn't be here today.
But this is really the essential matter, that we need to deal with it in terms of clinical judgment in addition to a statistical consideration. While the statistical consideration says well, do we choose the primary outcome at one year, you cannot reject your null hypothesis, and you will have to say that the trial by looking at the null hypothesis from the primary outcome, the one-year analysis has failed. But before you make that determination, I would urge you to consider all the other elements and the totality of the evidence from the trial.
First, there was a beneficial effect

actually apparent at one year if you look at all the other vision variables, not the three-line loss or the moderate vision loss which we chose as the primary outcome, but if you look at severe vision loss, vision loss below 20/200, or the average visual acuity scores, not matter where you look, there is some element of efficacy. Of course we will never conclude on these levels of significance in the absence of a primary outcome positive, that this is conclusive evidence. This was not conclusive evidence of efficacy but suggestive.

The angiographic data were stronger, .037 to .001 depending on which angiographic outcome you look at, but still, these were secondary variables, prespecified secondary variables. Having said that, all these vision outcomes, contrast and safety, angiographic outcomes were highly statistically significant, several of them below the .01 and some of them .001 if you look at the IDT analysis. All of them were highly significant, consistent, and all of them showed benefit at 24 months. So if we had chosen 24 months as primary time point of analysis, we wouldn't be here. If we had chosen other end points, at 12 months, maybe the visual acuity score changes, or the vision threshold of 20/200 probably

also wouldn't be here. So that's really the area of clinical judgment and expertise that, I think that's why we are here.

The other important point that people always ask, well, why you had two years, you have to wait two years for the VIP study and one year for TAP. We don't have data to formally say; we have several opinions and suggestions. There is a very simple explanation of that. As Dr. Bressler showed, the VIP patients started with much better vision than the TAP patients. The inclusion criteria for VIP were between 20/20 to 20/100, with an average visual acuity at the entry of 20/50, while the visual acuity for TAP was 20/40 to 20/200, with an average visual acuity of 20/100. That's several lines difference in terms of the entry criteria for TAP and VIP. A simple explanation is that the VIP patients having entered at a much better visual acuity, took a longer time to deteriorate to level at which we started to show significance. But that is a hypothesis that we need to look at the actual data and the analysis.

The other important point is the size and duration of benefit, and this did not come up in all the analysis of the CMS at this point in time, but it did come up in the March -- actually, this was the

only significant issue raised in the March 28th memorandum of the CMS, and that's why we still want to address it here. For the determination of the size and duration of benefit, they used the time to event analysis, or the survival of Kaplan-Meier analysis. And of course as cardiologists and medical oncologists by training, we all know that these are very valuable curves because they look at the entire totality of the period of the duration of time and it doesn't look at specific time points.

Having said that, these are valuable for definite permanent non-reversible events like death or cancer progression. If you look at vision outcomes, the effect on vision, it's variable. There are recoveries known for these events, so a patient reaching a three-line loss or a six-line loss today may recover in three months, and if you do a time to event analysis you will count that patient as an event, as a failure. You will not account for that patient when they recover. That's why these time to event analyses are not actually suitable for the vision outcomes because of the variability of scores. They are largely abandoned by the National Eye Institute in looking at vision outcomes in AMD trials. They basically use other methods to account

for the totality of the time effect, such as longitudinal analysis or the GEE model. And by the way, CMS in their statistical appendix ran a GEE model in which the treatment effect was significant, but that was not shared with you in the presentation today. But we have all these slides if you would like more elaboration on this point.

It was also not used by the FDA ophthalmology division for the same reason, in terms of a pivotal outcome for registration. That's why we didn't put any emphasis on that.

Having said that, we used then the CMS life table analysis to estimate the size of benefit, not for the median duration of effect, because that's not reliable. We estimated the size of benefit from the hazard ratio and the confidence interval. So even if you look at these analysis where the CMS said this is not significant and there is no benefit, the time to event analysis, looking at all the time to moderate vision loss, times to severe vision loss, this is three lines, this is six lines, or time of reaching a threshold that we know is important for the patient, which is the legal blindness threshold in the affected eye. All the hazard ratios are below one. It is true you could take the moderate vision

loss and say well, this is 21 percent reduction but it's not significant, but if you look at the time to severe vision loss, or time to a legal blindness level, they were significant. The hazard ratio doesn't include, or the confidence interval doesn't include one, and there is a risk reduction of 37 to 42 percent. 37 to 42 percent risk reduction in severe vision less and in vision threshold of less than 20/200.

So these are the time to event analysis and risk reduction, very similar by the way, to the risk reduction that Dr. Bressler had in his last slide. If you look at the proportion analysis, which is the prespecified analysis, there is about 38 percent risk reduction in the severe vision loss. Very similar data. So they don't really tell us something different from the proportion analysis.

Now what about the duration of benefit? Is that benefit just for a few months or that patient or for a year? We do not have long-term data from VIP. I would like to draw your attention that there is no reason to conclude that with more aggressive lesions, classic lesions, there is any reason to believe that occult lesions, which is slightly less aggressive, will be any different. This is the

visual acuity graphs over time between initially randomized verteporfin patients and placebo randomized patients, here in green. As you can see, there is a difference, of course it's statistically different, this is TAP.

And at two years we allowed all patients to enter into an open labeled extension, everybody was offered verteporfin, to look at the long-term effect and safety of the treatment. So starting from this point, everybody is getting verteporfin.

Despite the fact that everybody is getting verteporfin, it still, that benefit that was created by treatment was maintained if you look at the average visual acuity over five years. We believe that there is a logical explanation of why that vision level benefit was maintained over five years and we believe that that benefit is actually a permanent benefit to the patient, and I will explain why.

This will also answer, address the question of the cessation of treatment question that you have. The CNV lesions do not go active forever, they usually in their natural history, even if they are untreated, they dry out, they produce a terminal scar. And once they produce a terminal scar they

don't leak anymore and actually at that stage they reach what we call an end-stage vision. The vision is not going to deteriorate anymore. But f you are untreated, your end-stage vision is probably going to be very low, probably at the legal blindness stage or less. So that's what we're trying to prevent, trying to get the patient to an end-stage level of vision that is better than the legally blind, or at least higher than what they would have gotten if they were untreated. So that's what verteporfin essentially does, getting a terminal stage end vision of the patient that is beneficial. We believe that benefit, once established is permanent, because once we get a permanent scar there is no more loss of vision from the same lesion, unless the patient develops other diseases, but there will be no more loss from that lesion.

That also explains why the treatment frequency declines over time. We do actually have very good data on the frequency of treatment from the TAP five-year extension. These data were published in the TAP report number II and V, and the VIP report number II also published a two-year data of treatment.

We don't give treatment every three months

for everybody. It's every three months when there is active leakage. So when the leakage stops, there is no need for treatment.
So on average, what did that translate to?
It translated to the first year for both TAP and VIP, on average three treatments; the second, on average two treatments per year; and the third year, we only have data from TAP here because the only trial extension, and it is one treatment. This is the published data. The unpublished data that we have is that the fourth year, .5 treatment, and fifth year .1 treatment. It means on average, most of the patients are not getting any treatments after the third year. So that will also answer the question. These reports are available and published and actually provided to you in your package, and was available for the CMS.
DR. DAVIS: Dr. Azab?
DR. AZAB: Yes.
DR. DAVIS: I just want to do a time check, if I can. The CMS presentation was scheduled for 60 minutes and went for 75. Yours was scheduled for 65, and so from the interest of fairness, we would like to give you an extra 15 minutes as well, which means that you would need to wrap up in 20 minutes, you and your co-presenters.

DR. AZAB: Okay.
DR. DAVIS: So, I just wanted to give you that time check, and then we'll take a break.
DR. AZAB: Thank you, Mr. Chairman. I will try to go quickly on the other evidence, but I will be happy to answer any questions you have once, the session after the break.
The other was the approach to missing data, and I will try to go quickly. There was two misconceptions in the assumptions. We have more dropouts in verteporfin. We don't have more dropouts, we have the data as 14 percent and 13 percent. The loss of the vision carried forward doesn't treat everybody as success, it just carries forward the status that you have, whether it's success or failure, it will carry forward. It's recommended by the FDA for the IDT analysis and was prespecified in the original analysis plan, but the most important point in the approach to missing data is no matter how you look at the data, with or without LOCF, it actually looks the same.
This is the analysis in which we exclude all the missing patients from the analysis. Same thing. Difference of P values, all significant.
This is the analysis in which we even take a more

conservative approach, all the missing patients are failures. Essentially the same thing, considering the conservative nature of assigning everybody as a failure. You have one P value above .05 but still, it's still significant for the other criteria.

The CMS after six months of analysis in March, had specifically looked at this issue, and the conclusion in March was when the data were run without loss of vision carried forward, the results did not significantly change. Thus, it is unlikely that the use of LOCF bias the results in favor of the verteporfin group. That was the conclusion in March.

The other one is the interpretation of the VIP, the VIP is a repetition of TAP. This is a very strange assumption because both patients from the outset are completely different. VIP was designed to include patients who were excluded from TAP, it is completely different. Then they ignored all the treated patients, they just looked at the verteporfin, or the VIP untreated patients. They said they became TAP eligible. They became TAP eligible because they have now developed classic or the vision became worse, in other words, they said the untreated patients had disease progression. They had classic and the vision became worse, all this is

expected, they were untreated.
And then they made the assumption that we can assign to them visual acuity scores depending on the TAP results. I would leave to you the validity of all these assumptions, but we do have data on patients who converted to classic from the VIP trial. We do not need to make any assumptions. We looked at the VIP trial for those who developed any classic and those who never developed any classic.
You already see that verteporfin reduced the incidence of development of classic because you see more patients on verteporfin here in that group, but there is no consistent benefit in the patients who had any classic during the trial. All the benefit, and actually this is stronger in terms of difference from the overall occult, all the benefits come from the patients who never converted to classic. And you say well, because verteporfin stopped if from developing to classic, but that's a benefit, stopped them from progressing to classic, and also made the vision look better in patients who never converted to classic.
The safety, there is a risk of 45 percent of severe visual acuity decrease in the VIP trial. That event is already accounted for in the efficacy

analysis because in the efficacy we're already looking at the visual loss. As Dr. Bressler said, it's partially reversible and the long-term vision outcomes are not worse than no treatment. That remains to be the most risk for patients, is no treatment.

Summary of the response to the CMS issues, I hope I have clarified many of the misconceptions about the methodology. Addressed the study population subgroup analysis. The choice of the primary outcome which we admit, acknowledge that the primary analysis was planned at the wrong time point. The size and duration of benefit, we believe 20 to 40 percent reduction in moderate to severe vision loss is clinically relevant to the patients. The approach to missing data did not bias the results. And the results are not due to the patients converted to classic; actually, a watchful waiting approach would be harmful, and actually we have data from the VIM trial that shows that watchful waiting approaches harmful, and I will be happy to share that with you if you have any questions in the break.

The risk of acute severe visual acuity decrease doesn't outweigh the benefit. It's a small risk, there is recovery, and it is already accounted

for in the efficacy analysis.
This trial, of course there was a lot of misconception similar to the TAP trial, and the TAP and the VIP trials have been approved worldwide by regulatory authorities that scrutinize the methodology and by authorities who actually wrote the ICH guidelines, the European Union. It is approved in the occult in 71 countries for the classic indication and 41 countries for the occult indication, including the European Union, Australia and New Zealand.
It is not currently approved by the FDA, the occult indication, because it requires a secondary confirmatory trial which is well underway.
We have the support from the independent data and safety monitoring committee of this conclusion, of the American Society of Retinal Specialists, the American Academy, the study authors, and a round table of international experts.
I would like to leave you just with the conclusion that we hope to have shown you and clarified to you that the data on occult are strong, consistent at two years, all of them in planned variables, it's highly unlikely to give you the chance -- the benefit outweighs the risk, and the

size and duration of benefit are clinically relevant, particularly in the absence of any other therapy, and the data has gained international support. I am extreme grateful for your patience, Mr. Chairman, ladies and gentlemen of the panel. I would like to pass it on now to Dr. Packo.

DR. PACKO: Thank you. My name is Kirk Packo. I am the immediate past president of the American Society of Retinal Specialists. I am a retinal specialist in Chicago and practice at Rush University. I have no financial interest or any stock held in QLT and Novartis, nor ever had. I am an unsalaried member of the ASRS board of directors and my travel today is reimbursed by my society. I am not compensated for my time. I have no other conflicts to declare.

Who is the ASRS? We were formerly known as the Vitreous Society. It is the largest society of retinal specialists in the United States. There are 1600 members in all 50 states and 52 countries, 80 percent of which of the membership is here in the United States and as such, we feel we are the leading voice of retinal practitioners. The ASRS is able to ascertain preferences in preferred professional behavior in the retinal community through a variety

of activities, web sites, e-mail list servers, an annual written, which I will discuss briefly, a news magazine, and of course our scientific and practice management meetings.

I won't go through the time line of how our society has been involved in this process, but I do want to point out a few things. The ASRS, when we learned of the initial VIP study results, did at our own expense send out a national mailing to our membership alerting them to the potential benefit of this therapy, posted it on our web site. We were the original requestor to the CMS asking them to reconsider their coverage of PDT. And throughout the reconsideration process we were intimately involved with meetings in Washington with Administrator Skully and the coverage group.

As was stated, there are many people within the ophthalmic community that does conclude the value of photodynamic therapy for occult neovascularization, including the American Academy of Ophthalmology, the data monitoring committee of the trial, the editors and reviewers of the journal in which it was published, the HAO, the study investigators and as I said, our society through national core communication with the membership.

We do do an annual survey of our membership called the PAC survey. It's mailed out to the membership. We have a response rate yearly of approximately 40 percent and there are a couple questions of interest. In the spring of 2002, which was a few months after the CMS did conclude that they will not cover payment for PDT in occult, 37 percent of the membership was still primarily choosing PDT for the treatment of occult neovascularization, with basically an equal group matching with observation, and a smaller group looking for other continued unproven forms of therapy.

We asked this question just a few months ago and the statistic has not dropped despite our frustration with the socioeconomic problems related to the financial burden on our patients in treating. We are still, the primary choice is photodynamic therapy in the community for occult neovascularization. And from this and through the discussions at our meetings and list servers, we conclude that our membership considers this the standard of care for the treatment of occult neovascularization. Standard of care, as we all know, is what a reasonably competent physician would do in similar circumstances, it does not mean what

all of the physicians do or even a majority of the physicians do.
Medicare statutes mandate and we're here to discuss today what's deemed as reasonable and necessary for the treatment of disease, and we will consider two things to come upon that decision. The medical benefit to the Medicare population, which defines the health outcome better than the natural course of the disease as determined by the data analysis which we are reconsidering today, and the added value to the Medicare population. If there is no medically beneficial alternatives, then it is considered added value to the population.
We conclude, and I'm speaking for the retinal community, that the VIP trial is a well designed strong study. And as was stated, there is a difference between a weak study with a modest benefit and a strong study with a modest benefit. There are still to date no other proven alternatives. I think we are now into a statistical he said/she said as relates to whether or not this study is considered strong. We, however, do feel that it is.
We feel that the CMS has enacted a dual standard on coverage for PDT. They have accepted the TAP trial, although today have criticized that as a

weak trial as well, and yet continue to deny the VIP trial results. It is pointed out that classic and occult neovascularization in clinical practice is not black and white, it's very difficult to tell these two forms of macular degeneration apart, and the distinction is also very difficult angiographically. Our current position is that PDT is still commonly employed by our membership despite the CMS noncoverage for the ruling, and the end result of that is that the Medicare beneficiaries now bear that cost. A proven therapy thus becomes available to those who can afford it. The indigent who's declined therapy has a 50 percent higher chance of dropping to legal blindness, and it's the indigent who have the least resources capable of coping with that blindness, and our society truly does feel that that's a tragedy.

This noncoverage decisions ignores what we feel is a well designed trial, it ignores the conclusions of really the entire ophthalmic community. It noncovers the only available therapy we have available in 2003, and it rations medical care to Medicare beneficiaries.

My patients come to me asking me to help their vision with this condition. They don't come

saying do something for me by one year. We want to look for the long term and we hope the committee will join us in considering truly the totality of the evidence involved. Thank you for the opportunity to speak.

DR. DAVIS: Thank you.

DR. WILLIAMS: Good morning. My name is George Williams. I am a vitreal retinal surgeon and the chairman of ophthalmology at the William Beaumont Hospital in Royal Oak, Michigan. I am speaking on behalf of the American Academy of Ophthalmology. By way of disclosure, I do not have any stock or formal financial interest in any of the companies before us today. I have been an investigator in both the TAP and VIP trials. My expenses have been paid by the American Academy of Ophthalmology. I have previously addressed Administrator Skully on this issue as a representative of the American Academy of Ophthalmology.

As a service to its members and the public, the American Academy of Ophthalmology, representing over 16,000 ophthalmologists in the United States, has developed a series of guidelines called preferred practice patterns that identify characteristics and components of quality eye care.

These guidelines are particularly timely and appropriate as third party payers and government grapple with the need to maintain quality care in the face of cost containment and the traditional attitudes of academy members are challenged by changing patterns of health delivery and emerging market forces.

The preferred practice patterns represent quality eye care commensurate with present knowledge and resources. They are based on the best available scientific data as interpreted by an independent retina panel of knowledgeable health professionals, including practicing ophthalmologists, methodologists, and patient representatives. Any potential conflicts of interest are identified.

The preferred practice series of guidelines is written on the basis of three principles. First, each preferred practice pattern should be clinically relevant and specific enough to produce useful information to practitioners. Second, each recommendation that is made should be given an exclusive rating that shows it's importance to the care process. And third, each recommendation should also be given an explicit rating that shows the strength of the evidence that supports the

recommendation and reflects the best evidence available.
In 2001, the preferred practice pattern for age-related macular degeneration underwent a limited revision, which was prompted by the introduction of photodynamic therapy for age-related macular degeneration. Recommendations for care are based on the results of literature search rated in two ways.
First, the retina panel rated each recommendation according to the importance to the care process. This importance to the care process rating represents care that the panel believes will improve the quality of the patient's care in a meaningful way. The ratings of importance are divided into three levels. Level A, defined as most important; Level B, defined as moderately important; and Level C, defined as relevant but not critical.
The panel also rated each recommendation on the strength of evidence in the available literature to support these recommendations. These ratings are divided in to three levels. Level I includes evidence from at least one properly conduct well designed randomized controlled clinical trial; Level II includes evidence from well designed control

trials without randomization; Level III includes evidence obtained from descriptive study, case reports, reports of expert committees or organizations, and expert opinions such as consensus by the preferred practice panel. This system allows readers to appreciate the degree of importance the panel attaches to each recommendation and to understand what type of evidence supports the recommendation. The preferred practice guidelines developed by the retina panel are then reviewed by the preferred practice pattern committee. The guidelines are then subsequently reviewed by outside experts and relevant organizations. The final guidelines are then submitted to the board of trustees of the American Academy of Ophthalmology for approval. My subsequent comments are based on the age-related macular degeneration preferred practice pattern which was approved by the board of trustees of the American Academy of Ophthalmology in October 2001. In these guidelines, treatment recommendations are provided in Table 5 for various forms of age-related macular degeneration, and I believe you all have a copy of the preferred practice pattern guidelines.

On page 16, for subfoveal neovascularization with occult but no classic choroidal neovascularization, the treatment of recommendation is to consider PDT, particularly if lesion size is relatively small or lower levels of visual acuity are present. This recommendation was rated at the A-III level, meaning that the recommendation was high importance for clinical care and supported by Level III evidence.

In conclusion, the American Academy of Ophthalmology believes that photodynamic therapy with verteporfin in select patients with subfoveal choroidal neovascularization with occult but no classic choroidal neovascularization is a recommended treatment of high importance to clinical care. Thank you.

DR. DAVIS: Thank you. If we're going to stay on track with the schedule that I mentioned about 18 minutes ago, we have about another two minutes to go. I hate to ask you to be as brief as you can, but I need to do so. And we have received some submissions from you in writing in advance and the committee members have copies of those.

MR. CRAWFORD: I assume everybody is in front of me, right? Good morning. My name is

Charlie Crawford. I am the executive director of the American Council of the Blind, and I will talk fast in my two minutes. I have not -- we have not received nor have we asked for any economic benefit with regard to this. The American Council of the Blind is an organization that is most concerned about the benefit and quality of life for blind people. So, despite what a psychiatrist might say, I have no conflicts.

I am not a lawyer, I don't play one on TV. I'm not a doctor, I don't think you would want me doing surgery. What I am, though, is a person who represents tens of thousands of blind people who have had the experience of losing vision. And for our population, why would we even care, why would we even care about this drug? It's not going to do us any good. The fact of the matter is that we have had the experience that many people face in having to deal with vision loss.

And I note the amount of doctors on the panel, I note the amount of ophthalmologists here. I'm grateful for that. I'm grateful because at the end of the day, the decision you make is really about doing no harm, doing no harm to people who have to look at a future in which perhaps they will not be

able to experience looking at their grandchildren's faces, looking at a future in which vision loss robs them of a sense of engagement with life that cannot be replaced perhaps forestalled, perhaps treated with this therapy.

As blind people we don't spend our lives complaining and moaning and worrying about the fact that we're blind. We get on with it, we get on with it because we care enough about ourselves and about the society in which we live to make sure that we take care of ourselves and live productive lives.

But we do not deny, and the reason we are here is because we do not deny the fact that vision as a sense is an important thing that people should do and preserve.

So, we ask that you today when you make your determinations based upon the evidence, think about one question. Think about one question. Who do you trust? Do you trust the CMS people, do you trust the drug people, do you trust the lawyers or whoever makes their presentations? Do you trust me? Or in the end, do you trust your own judgment? Your own judgment that says to you, if I were treating this person, if I were involved with this person, what would I decide based upon the evidence I heard

today, remembering all the time that that person is relying upon you to make a judgment for them that will impact upon their ability to engage themselves with others, to be productive and to engage their quality of life.
And when and if they do lose vision, yes, the American Council of the Blind will be there, and we live happy lives, but we have not forgotten the value of what we once had. Thank you.
DR. DAVIS: Thank you.
MS. JALBERT: Good morning. This is a very auspicious group for a mother, a married woman, and someone who is threatened with blindness. My name is Lois Jalbert, I'm 77, and I'm a retired Medicare recipient and the mother of four, grandmother of two. I'm here today speaking on my own behalf. But that's not quite true, because when you start this business, you think of how many other might be in your same boat, so I think I'm talking of all people that might go blind.
I am a plaintiff in this litigation. My understanding is that this litigation is being financed by QLT and Novartis, and that they paid for my transportation in today's meeting. I have never served on an advisory committee, you can tell that

by the way I speak. And I have considered this topic before, but I was contacted by my lawyers of Arnold & Porter to discuss this topic, and that's about the only formal part of it all.

Of all medical experiences I have had, one included a long period in the hospital, the prospect of going blind was the one that really was unbelievable to me. The terror began in October 2001, and the highly highly regarded retinologist told me to eat seven to nine helpings of green vegetables a day, and that I would be blind in six months. I asked him to recommend another doctor, and he said I'm the best. And I said is that a personal opinion or a medical one, and he said personal. I said okay, I'm on my own. I left.

It took a lot of research. It took a lot of heartache. It took a lot of looking around and calling medical schools. I live on Cape Cod. I was even told incorrectly that Mass Eye and Ear wasn't working on wet macular degeneration. Unheard of.

But my first treatment, because I found Neil Bressler through the National Geographic, I saw a picture of a doctor operating and I called her and she said you want the guy downstairs, and that's how I got Dr. Bressler.

And I immediately, despite what all the very auspicious men said, I began feeling much better much quicker. On the way home I said to Russ, look, that's a stop sign. It was exciting, it was wonderful. And I'm here today in the hope that the government will soon come to the aid of the many tens of thousands of people who have occult macular degeneration, men and women who undoubtedly have feared, as I have, of the lifetime of medical traumas and who now cannot possibly afford to have the treatments that we need with OPT and verteporfin. In almost every visit to the Hopkins Eye Center, I happen to talk to at least one person who said I have been treated, I think it's going to be okay, don't you? Because you become a little fraternity as you're waiting there, it takes about a four-hour day. And I said well, I hope it does. And she said oh, it's go to, I don't have any more money. That is just heart breaking. And so, I urge the panel to recommend strongly to the powers that be that they approve the Medicare coverage of verteporfin treatment, and approve it quickly. And I thank you for giving me the opportunity to talk with you.

But I have something to say off the cuff.

I was dumbfounded at the idea of being blind, and I was angry, and then I got sad. My husband can tell you I got surly. Oh my, it was tough. And then I got depressed. Finally I sat myself down and said what is it, Lois, that's driving you nuts? And it finally occurred to me. Options. I'm going to face a life of options. You face the choices but I get a life sentence. And you know, we Americans love options. We want little cars, we want SUVs. If we have ice cream, and it's vanilla and strawberry, or it's kiwi and mango. Most of the young women are wearing their dresses above their knees, I wear mine down below my ankles. Those are options. But my options were being cut off completely, and I pray that some of the options will be left for women to see, men to see, little children to see. Mr. Bush says it costs $6 million a month in Iraq, but not to worry, it's only 1 percent of our national budget. What's it going to cost the rest of us seeing for whatever period of time we can? Thank you.

DR. DAVIS: Thank you very much. I would like to thank all the presenters on behalf of the requestor, and we will take a ten-minute break. We are about 40 minutes behind schedule, we'll try and make that up, but I would like to ask the members of

the committee to try and be back here promptly in ten minutes.
(Recess.)
DR. DAVIS: I understand that 13 people are scheduled to speak during this first public comment period, which is listed on the agenda as scheduled public comments, and as we follow the agenda then we will have an opportunity for some questions from the members of the committee for the presenters, and then we will have a short period of time for open public comments before lunch. So we will see how we do in trying to fit all of that in before lunch.
As I think I said, about 13 people have been scheduled to give public comments during this next session, so we will proceed immediately with the first one, and I would ask each of you to be as concise as you can, given that we're already behind schedule. And if you could limit your comments to three to four minutes each, we will be indebted to you. Please proceed.
Let me also remind you that we would like each presenter to indicate any conflicts of interest that they might have.
DR. HOLROYD: Thank you, Mr. Chairman and

the committee. My name is Ken Holroyd, and I am speaking on behalf of Genaera Corporation, where I am executive vice president and chief operating officer. Genaera Corporation has sponsored my visit, as I am an employee of the corporation and stockholder in the corporation today. Our interest in this area is around our mission, which is developing new medicines for serious diseases. We do feel that wet age-related macular degeneration is a serious disease worthy of our efforts and mission, and we certainly support the reimbursement of treatments for what macular degeneration that provide clinical benefit to patients.

In order to give some perspective of an early investigational therapy for choroidal neovascularization associated with age-related macular degeneration, I wanted to share with you this morning our interim results of a Phase I-II study or our compound squalamine for the treatment of choroidal neovascularization associated with age-related macular degeneration.

At the end of therapy or four-week period in the two-month period which I'd like to share with you today as, again, an example of an early investigational therapy, anti-angiogenesis therapy

for wet AMD. The study enrolled 40 patients, and as has been widely discussed this morning, used the ETDRS scoring system for visual acuity, along with ocular angiography, of which I will show you a few brief examples, and photography. We did the study with Hugo Quroz-Mercado, with the advice and participation of Dr. Charles Garcia and Gholam Peyman.

40 patients were enrolled, and these are the results at the four-week and two-month periods. We had visual improvement of three lines or better in one-third of the patients at both time points and stabilization, that is, minus two to two-line improvement in all but one remaining patient at the two-month time point. The range of improvement, a range of line change was from minus three to plus eight lines. The patient who had eight lines improvement had a resolution of re-central scotoma that allowed her to return to work as a computer technician, and the median visual acuity was 20/80 and 20/100 at those time points, along with improved vessel leakage and subretinal blood improvement on angiograms.

These results were present in both the classic subtype and the occult subtype. As the drug

was given intravenously, it's able to go to those activated vessels in both subtypes through the circulation.

And this is just a further breakdown where we can see among the completely occult patients, of which are the subjects of today's meeting, there were 7 percent of those enrolled in the study, and 48 percent were predominantly occult with some classic component, also known as minimally classic.

If we look at all affected eyes, which includes second eyes, we had similar results with a nice range of patients with improvement or stabilization of vision at these time points. And if we look at second eyes unaffected by wet AMD as an internal control for the study, we see much less of a change, that is, they are expected to stay stable over time.

These are just some examples of angiograms with our therapy, looking at four time points. On the upper left, the baseline condition. You can see the AMD lesion in the center of the photograph. Then at the four-week time point on the upper right, and then after squalamine therapy is stopped, and follow-up at the two-month and the four-month time point. In this patient there is an example where the

lesion has some improvement angiographically, and that continues up to the four-month time point, the long intracellular half-life of our compound. We're using this follow-up period to design the best maintenance therapy for the compound that we will use in future studies.

This is an example where at the four-month time point after some improvement, there is progression of the lesion and maintenance therapy at probably the four to eight week interval would be beneficial for this patient.

This is another patient where we had some improvement in lesion that continued through four months with our initial four-week therapy.

So, in our view, this is an example of an anti-angiogenic therapy as part of a newer approach in early investigation for wet AMD. However, we have these results and in conclusion, we believe this less invasive compared to intravitreal therapy alternatives may avoid complications, allow safer long-term maintenance therapy, allow the second eye to be treated at no additional risk, and we look forward to demonstrating efficacy and safety for improvement or preservation of vision. Thank you for your attention.

DR. DAVIS: Thank you. Dr. Kim.
DR. KIM: Thank you. I would like to thank the committee for inviting me to speak at this meeting today. My name is Robert Kim, and I am the chief clinical scientist for ophthalmic medicine at Genentech, and I appreciate the opportunity to present data today pertaining to our research in wet AMD.
I'd like to start by making the following disclosures: In addition to the volunteer faculty position I hold at UCSF, I'm employed full-time by Genentech and am paid a salary. I own Genentech stock and my travel costs for this meeting were paid by Genentech. I do not sit on any advisory committees or panels that have considered the subjects of today's meeting. That said, I would like to begin my presentation about Genentech's program.
Genentech's therapeutic strategy is based upon inactivating a protein known as vascular endocubial growth factor, or VEGF for short. It's a very strong stimulator of angiogenesis, and several lines of evidence have implicated VEGF in wet AMD.
Genentech's anti-VEGF program uses monoclonal antibody technology to bind and thereby inactivate VEGF. A humanized monoclonal antibody against VEGF,

it was originally developed for cancer, is unfortunately too large to penetrate through the retina and inject it into the eye. Consequently, efforts were undertaken to isolate just the portions of the antibody that binds to VEGF, and that portion is known as an FAB fragment. And in a subsequent step, the affinity of that fragment for VEGF was enhanced. The molecule at this point has several names. Its chemical name is ranibizumab; its nickname is rhu-FAB V2, which stands for recomitant human FAB fragment, version 2, and its brand name is Lucentis. The drug is administered by injection into the vitreous cavity in the back of the eye.

Genentech has an active clinical development program for ranibizumab in the area of wet AMD. A number of Phase I/II studies have been completed and two Phase III programs are currently underway.

Our first study, the 1770 study, involved 27 subjects with AMD, and taught us that the maximum tolerated dose is 500 micrograms, with the higher doses being associated with intraocular inflammation. All of the subjects in this single-dose study maintained at the end of the three-month study period, ended up with visual acuity that was similar

to or improved from baseline.
The 1770 study set the stage for the 2128 multidose study. The purpose of the study was to evaluate the safety, tolerability and activity of multiple doses of ranibizumab. The study population included subjects with predominantly classic CNV, minimally classic, and occult only CNV, and subjects who had had prior photodynamic therapy.
The study had two parts. In part one, the 64 subjects were randomized to one of three treatment groups. The first group consisted of a group of a series of four injections of 300 micrograms injected four weeks apart; the second group consisted of an injection of 300 micrograms, followed by a series of 500 microgram injections injected four weeks apart; and the final group was the usual care group which depending on the lesion type, consisted of either observation or photodynamic therapy.
Subject were then evaluated at day 98, or approximately three months and assessed, and subsequently subjects were offered the option of participating in the second part of the study in which for the two treatment groups, they continued to receive treatment and in the case of the usual care group, they were offered the opportunity to begin to

receive drug in one of the two doses being studied. Ranibizumab was well tolerated in this study with the most common adverse event being transient intraocular inflammation which was reversible and self limited. We did see three drug related serious events, which included endophthalmitis, epeitis (phonetic), and central retinal vein. All conditions have resolved, however, and all subjects recovered their premorbid level of visual acuity.

At the end of part one of the study, the usual care group lost an average of 5.1 letters on the ETDRS calibrated visual acuity chart. In contrast, the subjects receiving 300 micrograms of ranibizumab gained an average of 8.8 letters, and the 500 microgram group gained an average of 9.1 letters. At this point in the study, the subjects were offered the opportunity to enter part two of the study. In the group of subjects who received ranibizumab from the beginning and elected to continue and maintain and were seen for the full six-month study period, the visual acuity benefits seen at three months appeared to be maintained at six months. In the group of subjects in the usual care group that elected to continue on into part two of

the study, the average visual acuity appeared to improve once they began to receive the series of four injections of either of the two doses of ranibizumab. In terms of lesion subtype, we only have data at this point for the Phase I results at day 98 but we observed that an improvement in visual acuity was seen both for the predominantly classic patients, as well as the subjects with minimally classic or occult only CNV.

At this time Genentech is currently enrolling a Phase I/II study called the focus study. The purpose of this study is to evaluate ranibizumab and verteporfin photodynamic therapy as combination therapy for the predominantly classic form of CNV. While we have been encouraged by our Phase I and II experience, we have to keep these results in perspective because these studies were small, of short duration, unmasked and in some cases uncontrolled. Consequently, Genentech is currently enrolling two large double masked Phase III pivotal trials, one targeting minimally classic and occult only disease, and one targeting predominantly classic disease. It's only until we get the definitive results from these studies, which are currently enrolling and will be of two years' duration, that we

will be able to make any kind of final judgment regarding the safety and efficacy or ranibizumab in wet AMD.
So in conclusion, we're making great strides in understanding the science underlying wet AMD, and more importantly in developing therapies that may help patients live longer and better lives.
It is therefore important to ensure that patients will have access to this and other breakthrough therapies coming down the pike. Otherwise, these scientific discoveries are fruitless.
Thank you again for inviting me to present here today as you consider these important issues.
DR. DAVIS: Thank you.
MR. THOMAS: Good morning. My name is Will Thomas. I am with the Gray Panthers National Office in Washington, D.C. I have no conflicts and my travel here was paid for by myself.
Gray Panthers is a national organization of intergenerational activists. We are age and youth in action. I am pleased that the Medicare Coverage Advisory Committee has convened this session so that together we might right a wrong today. The National Institutes of Health estimate that 5 percent of those over 65 has some vision loss due to age-related

macular degeneration. In seniors, it is the most common cause of irreversible blindness in the developed world.
The wet form of AMD is fortunately amenable to ocular photodynamic therapy, OPT, with verteporfin, which we all know, recommended by both the American Academy of Ophthalmology and the American Society of Retina Specialists. OPT with verteporfin is a proven effective treatment.
AMD is characterized by a progressive loss of central vision. If the health and well being of seniors were in the center of our vision, the right decision, Medicare coverage of OPT would have been settled long ago. Persons on fixed incomes would not require a coin flip, a 50 percent chance of whether or not they were going to lose their vision through a diagnosis with this disease. CMS made the wrong decision.
Fortunately for America's seniors, we have the right to challenge wrong decisions made by our government. This wrong can be made right. Gray Panthers urges that Medicare coverage of OPT with verteporfin be endorsed. Let's keep the health of our seniors in the center of our vision. Thank you.
DR. DAVIS: Thank you. Next please.

00150

MS. SIEGEL: My name is Ellen Siegel. I am a Medicare recipient. I have no stocks and I paid my own way.

I have had several illnesses. I have had breast cancer, I had chemo, and two days later went back to work. I had radiation at eight in the morning, went to work. I had my knees replaced because I have an arthritic condition. I did the therapy, went back to work. I did insurance physicals.

This is the only condition that causes me to cry. None of the rest of them affected me like this. I'm sorry, I have difficulty with this. It took away a very important part of my life. I'm 68 years old. I can no longer drive. I don't work anymore. I'm fortunate that I have a husband who can take me around and read for me.

I was treated at Shea Institute, I live near Philadelphia, with a laser treatment that was not PDT. My right eye, which was my better eye, was badly injured. I was fortunate. My son looked on the Internet and found Dr. Bressler. I'm a patient of Dr. Susan Bressler, and I'm grateful for whatever vision I'm able to maintain, because I can walk around and I can see some. I hope that none of you

ever face the choices that I have had to make. I have a house; if I have to sell it to pay for this treatment, I probably would, because eyesight is that important. Thank you for your time.

DR. DAVIS: Thank you, Miss Siegel.

MR. HERMAN: Hello, my name is David Herman. I'm executive director of the Seniors Coalition, Springfield, Virginia, also on the board of the AMD Alliance. I have no stock conflicts, and the Seniors Coalition paid my expenses to come here today.

The Seniors Coalition is a nonprofit 501(c)(4) nonpartisan education and issue advocacy organization that represents the interests and concerns of America's senior citizens at both the state and federal levels. Our mission is to protect the quality of life and the economic well being that older Americans have earned, while supporting common sense solutions to the challenges of the future.

We're pleased to have this opportunity to address this advisory committee for the Centers for Medicare and Medicaid Services.

We're here today to urge you to reconsider your decision to exclude Visudyne as a treatment covered by Medicare. Your decision directly impacts

patients suffering from age-related macular degeneration, a progressive eye disease that's the leading cause of blindness in individuals 50 and older. Medical research and experts in the field, including the American Academy of Ophthalmology and the American Academy of Retina Specialists agree that OPT with verteporfin is the most effective medication available for treating patients with the most serious form of AMD, and that is wet AMD.

According to the AMD Alliance, although wet AMD accounts for only about 15 percent of all its cases, it is responsible for 90 percent of severe vision loss associated with the disease. Wet AMD evolves rapidly and the majority of patients can lose their central vision within a few weeks to a few months of being diagnosed. For seniors diagnosed with wet AMD, availability and timing of treatment is very important. Every day without proper treatment is an additional day of irreversible loss of sight. That's why it's important for you to act quickly or to make OPT with verteporfin available to Medicare participants.

We are not able to explain to our seniors that while those Americans with the financial means to pay for their own treatment will keep their sight,

those who depend on Medicare will not get this innovative treatment and therefore, they will go blind.
We've got a spokesperson that works for us that's 81 years old and travels the country on senior issues. And she has AMD. She also has private insurance, she's being treated and she's doing pretty well. She's got a sister who's 91 and going blind at the speed of light, paraphrasing that. She only has Medicare. We've come to the stage where the size of your wallet determines the size of your treatment, and that's just plain wrong. Thank you.
DR. DAVIS: Thank you.
MS. BORENSTEIN: Hello. My name is Audrey Borenstein and I am a Medicare beneficiary speaking on my own behalf. I do not have any type of financial interests in the American Society of Retina Specialists, in Novartis or in a competitive company, and I have not received any financial aid from any of these companies on my behalf. My understanding is that this litigation has been paid for by QLT and Novartis, and they have paid for my transportation to come here today.
There is an old cliche that goes there are none so blind as those who will not see. That does

not apply to me and tens of thousands of those affected with macular degeneration. We are not those who will not see, we are those who cannot see. To me and other suffers of macular degeneration, it is the federal government who will not see. This is my story.

About three years ago I went to get a new prescription for eyeglasses and was shocked when I was told that first I had macular degeneration, and second, I may never be able to drive again. In an instant, and I mean an instant, I could perceive the loss of mobility, the loss of independence, and the loss of my sense of vision that had always been so precious to me.

I became a patient of Dr. Morton Goldberg at Wilmer at Hopkins. My right eye had one kind of macular degeneration called a classic, and my left eye a different kind. For my right eye, I had six treatments of PDT, a special therapy, with the goal of stopping the progress of the degeneration and hopefully delaying a recurrence. This was tremendously successful to me. I even got a small improvement to my vision, and Medicare paid for it.

The doctor then suggested that I might want to have the same treatment in my left eye.

However, Medicare would not fund this. I paid out of pocket $2,500 at first because fortunately I was financially able to do this. My results again were favorable. The doctor was delighted, almost as delighted as I have been.

Is my vision good? No. But I have been able to maintain a large percentage of my independence, of my ability to care for myself, and my passion for reading and for playing bridge. I could afford to pay, but I cannot afford to pay for five more treatments. And how about the majority of people who cannot afford to pay at all for this procedure. Must they wait until they become totally blind, then go to medical assistance to get the help they need? This costs the federal government much more than funding a procedure that may help so many of us who have the same independence that I enjoy.

Yes, I feel funding the procedure for both types of macular degeneration is the humanitarian thing to do, and what should impress the government more is that funding that procedure is the most efficient and most practical thing to do.

The government has a choice, both humanitarian and practical, if only they will learn to see. So many of with macular degeneration do not

have that choice, we cannot see.
MR. DAVIS: Thank you. Let me ask all the speakers to please be careful and avoid tripping over the cords. We apologize for the obstacle course that you have to walk through to get to the microphone. Please proceed.
DR. BALL: Good morning. My name is Dr. Josephine Ball. I am representing the health committee of the Baltimore NAACP as the chair of that committee. I have not received any funding and I have no interest in any of the companies involved.
We strongly urge the Medicare Coverage Advisory Committee to recommend Medicare coverage for ocular photodynamic therapy for patients with AMD or occult age-related AMD. As you are aware, the National Association for the Advancement of Colored People is the nation's largest and strongest civil rights organization, with 2,200 affiliates covering all 50 states, the District of Columbia, Japan and Germany. The NAACP's principal objective is to ensure the political, educational, social and economic equality of minority group citizens of the United States and to eliminate racial prejudice. We seek to remove all barriers of racial discrimination through democratic processes.

Since this hearing is occurring in Baltimore, the Baltimore City NAACP is compelled to voice its dismay that Centers for Medicare and Medicaid Services would deny coverage of a medical procedure that is so vital in ensuring that all Americans, especially minority groups, will have a fighting chance to prevent vision loss and its disabling condition.

We do not claim to be medical experts, however we do know quite a bit about fighting for equity in health care. It is patently discriminatory that ocular photodynamic therapy is only for those who can afford it. The minority, elderly and poor, a large number of whom are our constituents, disproportionately rely upon Medicare as the means to pay for the ever escalating costs of medical services. There is sufficient research and case studies to clearly support the efficacy in the treatment of wet macular degeneration with occult lesions. So the real question is how many poor and elderly minorities must needlessly lose their sight before CMS expands Medicare coverage for therapy.

As the NAACP Washington bureau said in its March 12, 2002 letter to HUD Secretary Skully, this therapy is the only effective treatment for this

disease and is considered the standard of care by the American Academy of Ophthalmology and Retinal Specialists nationwide. Without Medicare coverage, African American seniors, as well as seniors who need but cannot afford this therapy, will needlessly lose their sight. If the Centers for Medicare and Medicaid Services do not reaffirm their decision to expand Medicare coverage to include AMD patients with occult lesions, then only those seniors with sufficient resources to combat this enemy of vision will be able to receive this crucial treatment.
It is ironic that over than 100 years ago, African American chemist Percy Julian discovered the first treatment for glaucoma, and yet today, we, African Americans will not be able to benefit from vision saving treatments pioneered by Percy Julian, and others, simply because they have to choose between eating or staying warm or seeing.
We strongly urge you to join the growing and diverse chorus of voices that call for the expansion of Medicare coverage for the use of this treatment. To paraphrase a phrase that those of us in the civil rights struggle know well, coverage delayed is coverage denied. Thank you.
DR. DAVIS: Thank you. Next please.

MR. LEVINSON: My name is David Levinson. I'm a real estate developer developing in four states. I'm speaking on behalf of myself. I have no conflicts. I paid my own expenses. From 1985 until 1993 I served as the insurance commissioner of the State of Delaware and in that capacity served on the Health Committee of the National Association of Insurance Commissioners and on the HCFA Medicare Supplement Commission under Presidents Reagan and Bush.

You have heard today from distinguished practitioners regarding the science of treating AMD and more particularly, AMD with occult lesions. I would like to point out that from a broader public policy standpoint, the cost to society of an individual's loss of vision transcends if possible, even horrors suffered by the patient. The retention of even minimal vision and accompanying self sufficiency saves society far more than the cost of the treatment in question. In an effort to provide the most efficient health care to our country's citizens, whether through private insurance or public insurance such as Medicare, every effort should be made to support individual self sufficiency, and in the instant case that surely means supporting a

decrease in the risk of complete loss of eyesight through providing OPT to those patients suffering from AMD with occult lesions.

But I'm also testifying here today as someone who is currently suffering from AMD with occult lesions. After undergoing two operations on my left eye for a detached retina, I was alarmed last year when I began to lose vision in my right eye. I was fortunate in that my cousin, Professor Daniel Finkelstein, formerly served as chairman of the department of ophthalmology at the Wilmer Eye Institute at the Johns Hopkins University, where he continues to practice today. He observed the deterioration of my eyesight for many months before concluding, in consultation with Dr. Neil Bressler, from whom you have heard earlier today, that OPT represented the best chance that I had of retaining some eyesight in my right eye.

I cannot emphasize too strongly to you what losing my vision would mean to me and my family. Not only would my personal quality of life become marginalized, but also, I cannot conceive of how I could continue to operate my real estate development businesses with all of their employees, or even meet my legal responsibilities throughout the country.

I'm fortunate in that I can afford the $2,500 per treatment that OPT costs, and even the $15,000 cost of the six treatments that are typically required. But how many of our citizens are that fortunate? It is virtually inconceivable to me that anyone would argue that it is all right to allow Medicare recipients to go blind because it took two years rather than one year to prove the effectiveness of OPT. Many private insurers have already recognized the appropriateness of covering this treatment. Aetna, Humana, Capital Health Plan, Anthem of Virginia, Trigon, Partners Health Plan, Physicians Health Plan, and Blue Cross under Blue Shield plans of Arkansas, Georgia, North Carolina, Kentucky, Washington, Oregon, Arizona and California all cover this procedure. I am here today to ask that Medicare make the decision that is both cost effective and compassionate, and agree to cover OPT for patients suffering from AMD with occult lesions. Thank you for permitting me to comment today.

DR. DAVIS: Thank you. Next please.

MS. BERGER: Good morning. I'm Helena Berger. I'm the chief operating officer at the American Association of People with Disabilities. I have no conflicts of interest, I paid my own expenses

for today's meeting. Thank you for giving the American Association of People with Disabilities, better known as AAPD, the opportunity to testify about the importance of providing Medicare coverage for ocular photodynamic therapy (OPT) with verteporfin, trade name Visudyne, as a treatment for occult age-related macular degeneration.

AAPD is a national membership organization promoting political and economic empowerment for all citizens with disabilities in the United States. With more than 50,000 members around the country, AAPD is the largest national cross-disability membership organization in the U.S. As you know, visual impairment is one of the ten most frequent causes of disabilities in America. AMD, which involves the destruction of a person's central vision, is the leading cause of blindness among people over the age of 50. Early diagnosis and treatment of AMD is key because once vision is lost due to the growth of abnormal blood vessels, it cannot be reclaimed by treatments.

Visudyne is currently the only effective therapy available to treat this disease and arrest vision loss. While Medicare currently covers this

therapy for treatment of AMD with classic lesions, it does not cover it for AMD with occult lesions, leaving beneficiaries diagnosed with this form of the disease without treatment option.

We cannot put a dollar value on having one's sight, but we do know that there are both considerable personal and societal costs associated with blindness, especially for older Americans. According to National Eye Institute Director Paul A. Sieving, M.D., Ph.D., "Blindness and vision impairment represent not only a significant burden to those affected by sight loss but also to the national economy as well." Medicare coverage of Visudyne therapy can help alleviate these problems. Access to this therapy will allow many seniors to significantly slow sight loss and retain very usable vision, along with their independence.

To be honest, I am baffled by the lack of Medicare coverage of this therapy to treat AMD with occult lesions, as I understand that both the American Academy of Ophthalmology and American Society of Retina Specialists consider it the standard of care for this serious ocular condition.

I urge you to resolve this issue immediately and ensure that all Americans, not just those who can

afford it, have access to this vision saving therapy. The sooner CMS's decision is reviewed and reversed, the fewer beneficiaries will suffer harm. Thank you for your consideration.

DR. DAVIS: Thank you. Next please.

MS. WARREN: My name is Stella Warren. I am a Medicare beneficiary speaking on my own behalf. I do not have any type of financial interest in Novartis, QLT, the American Society of Retina Specialists, or competitive companies, and I have not received financial support from any of these companies. I was a plaintiff in the litigation that led to this hearing. My understanding is that this litigation was QLT and Novartis, and that they paid for my transportation to today's meeting. I have never served on an advisory panel that has considered this topic before, but I was contacted by my lawyers at Arnold & Porter to today's meeting to discuss this topic.

I am 83 years old. My income consists of Social Security and a small pension from my late husband from Westinghouse. In 2001 I was diagnosed with AMD with occult lesions and began to see Dr. Bressler for treatment. Dr. Bressler recommended, and I received two treatments of OPT

with verteporfin and after these treatments, I noticed a great difference in my eyesight. I couldn't see the fine print, and after the second treatment, I could at least see with the magnifying glass. Because of these treatments, I can still see with a magnifying glass, and do all my own housework and everything. However, Dr. Bressler recommended a third treatment which was scheduled in April of 2003. However, each treatment is $1,800, and this simply is too expensive for me. I cannot afford it. I cancelled the appointment and currently do not receive these treatments. Please make this treatment available under the Medicare program. Like other low income persons with occult AMD, the longer I can see the longer I can live independently. Thank you.

DR. DAVIS: Thank you.

DR. LEMUS: Good morning. My name is Dr. Gabriela Lemus. I am the director of policy and legislation for the League of United Latin American Citizens. I have no financial interest in this matter, and I provided my own transportation. LULAC is the nation's oldest and largest Latino civil rights organization in the United States, having started in 1929. As our mission, we advance the economic condition, educational

attainment, political influence, health and civil rights of Latinos throughout the United States through our community based programs operating in more than 600 LULAC councils nationwide and in Puerto Rico. As a key component of our legislative agenda, we have long been advocating for the expansion of state and federal funding, including Medicare, to meet the medical needs of our Latino senior citizens. Today's hearing is very important to us.

As you know, by the age of 65, one in three Americans suffer from some form of vision threatening disease, and according to the American Foundation for the Blind, Hispanics in particular have long had high rates of visual impairment as a result of geographical and cultural barriers to information, health care and rehabilitation. And because AMD is the leading cause of blindness in older Americans over the age of 50, LULAC has been working to increase patient education programs in the Latino community throughout the United States to secure Medicare coverage of vision screenings for retinal diseases such as macular degeneration, glaucoma, and diabetic retinopathy, as well as to expand Medicare coverage of Visudyne therapy. Like so many others here, we were deeply disappointed to learn that the

Centers for Medicare and Medicaid Services rescinded their original decision to authorize Medicare coverage of Visudyne therapy for patients suffering from AMD with occult lesions.

LULAC is strongly committed to our elders and their well being. Recent census data indicates that over 14 percent of the 38.8 million Hispanics in the United States are over the age of 50. While we know that AMD is an incurable eye disease, we also understand that timely treatment can slow down the vision loss and help to preserve sight. With so many Latino elderly relying solely on Medicare for insurance protection and so many of our Latinos in general are uninsured or underinsured, coverage of Visudyne therapy for patients suffering from AMD with occult lesions is imperative.

The availability of Visudyne therapy is a welcome treatment and Latino seniors should not have to decide whether to pay out of their pocket, and I'm not even sure that they can, so many of us make under $40,000 a year for our family income. LULAC urges the panel to quickly conclude that Medicare coverage for the use of Visudyne treatment is fair and reasonable for our nation's elderly and that the Department of Health and Human Services should

partner with public interest groups like those represented here today to embark on an aggressive public education campaign, and I would include in multiple languages. Thank you.

DR. DAVIS: Thank you.

DR. ROSENTHAL: Good morning. I am Bruce Rosenthal, chief of the low vision programs at Lighthouse International. I am the immediate past chair of AMD Alliance International, as well as being the chair of its scientific advisory board. I'm also an adjunct professor at Mount Sinai Hospital. I don't own stock or have any financial relationship with any of the companies. I do represent the Lighthouse and the AMD Alliance, which have received unrestricted educational grants from Novartis. The Lighthouse paid for me today.

Macular degeneration has a profound effect on visual function. Significant vision loss from macular degeneration may result in the loss of one's livelihood, a loss of self esteem, a loss of independence, as well as lead to clinical depression. It is therefore imperative that we use available medical treatments as well as vision rehabilitation to prevent vision loss and maintain independence. There are a whole constellation of

components that go into making up vision. Visual acuity is perhaps the most common one that comes to mind. Visual acuity is the ability to distinguish details of objects as well as being a measure of clarity or clearness of vision. While visual acuity is an important measure of visual function, it describes just a single aspect of vision. There are several other essential components of vision. These include contrast sensitivity function, visual field, fixation, glare recovery, stereo acuity, and color perception.

Visual acuity is, however, one of the major components of visual function. It affects every aspect of our daily lives. Even the slightest decrease in visual acuity will have a profound effect on visual performance. Reduction in central visual acuity, for example, may affect a person's ability to undertake many activities, including socializing, reading, driving, watching television or playing golf.

Contrast sensitivity on the other hand, is a little-known component of visual function outside of the professional eye care community, but contrast sensitivity is in many ways just as or more important than visual acuity in daily activities. Contrast

00170

sensitivity is a measure of the ability to see low contrast patterns. It has been recognized for its importance in influencing the quality of vision. Poor contrast makes the world appear hazy or washed out, and can lead to difficulties in driving at night or in rain or in fog. It is also important in judging distances, walking down steps and recognizing faces, as well as finding a number in the directory or reading instructions on a medical container. Poor contrast sensitivity may also lead to a loss of spatial awareness and poor mobility, and older adults who have poorer levels of contrast sensitivity have been found to experience falls more often than those with good contrast sensitivity function. Patients with reduced contrast sensitivity also have severe problems in reading. Even reading the newspaper may be impossible without special low vision devices because the print is just too light.

Macular degeneration has been shown to cause scotomas as well. These are areas of reduced or absent central retinal sensitivity in the visual field, which may be located centrally or paracentrally for patients with AMD. Scotomas also have a major impact on the performance of everyday activities and have been reported in 91 percent of

low vision rehabilitation patients. The presence or absence of a central or paracentral scotoma is a much more powerful indicator and predictor of reading problems, more so than visual acuity. It has also been shown that patients with visual impairment are at risk for significant levels of emotional distress and depression.

DR. DAVIS: Dr. Rosenthal, could you please wrap up quickly? Thank you.

DR. ROSENTHAL: In summary, patients with occult age-related macular degeneration should be afforded an opportunity to receive treatment. The benefits to the patient as well as society far outweigh any costs involved.

DR. DAVIS: Thank you.

MR. GARRETT: Good morning. I am Daniel Garrett. I am from Prevent Blindness America, and I am also on the board of directors for the AMD Alliance International. I have no financial interests or involvements with any of the companies represented here today. My organization, Prevent Blindness America paid for my transportation here. As I mentioned, Prevent Blindness America is the organization that I work for as senior vice president. We have more than 5,000 volunteers and we

touched the lives of nearly two million people last year through our vision education and screening programs. I am pleased to speak today in support of Medicare coverage for ocular photodynamic therapy with verteporfin for the treatment of AMD with occult lesions. Prevent Blindness America is the nation's leading eye health and safety organization, dedicated to fighting blindness and saving sight.

There are more than 1.7 million Americans that have AMD today in this country. The statistics are staggering and with the aging adult population, with the baby boomers growing older at every moment, the number is only going to increase. AMD is the leading cause of blindness among seniors. The disease's causes are not yet well understood, and AMD often progresses quickly and causes such dramatic vision loss that a patient becomes legally blind within a short time after diagnosis, as we heard earlier this morning. Therefore, early diagnosis and intervention is absolutely critical to preserve eyesight, one of the most precious senses of the Medicare population.

It's important to point out that blindness is one of the most feared disabilities in this country. The cost of blindness is estimated to be

more than $4 billion annually. This staggering figure will only increase if more is not done in the prevention, treatment and research of eye diseases, in particular AMD. While there is no cure for AMD, there is one proven and effective therapy available, the treatment we have been speaking about today. It treats the wet form of AMD, which is the most rapid and severe central vision loss, OPT with verteporfin. This therapy can and has helped significantly slow sight loss, allowing people with AMD to retain both their vision and quality of life.

In addition, we understand it is considered the standard of care of patients with AMD with both classic and occult lesions, that's the type, of course, that is the focus of this meeting.

Today the administration has created a tacit policy whereby a privileged few can afford this sight saving therapy which would allow them to live independently and enjoy life without the needless suffering from progressive vision loss and blindness. It's inconceivable that potentially millions of Medicare beneficiaries will lose their sight and perhaps their quality of life because they are unable to afford a proven effective treatment. This needless blindness will also end up costing us taxpayers in the long

run.
Please carefully consider the evidence here today and agree with our own Health and Human Services Secretary Tommy Thompson, and I do quote, "By expanding access to this important new treatment, we are improving the quality of life for many Medicare beneficiaries." That was our Secretary of Health and Human Services. Thank you for allowing me to speak today.
DR. DAVIS: Thank you. Five people have requested to give additional public comment for this item on the agenda that's labeled open public comments, and it doesn't make sense to me to split up these two items on the agenda for public comment, so we're going to proceed quickly to those five individuals. I will ask you if you could limit your comments to two to three minutes, and then we'll decide where to go from there. And again, state your name and whether you have any conflicts.
MS. HYATT: Hello. My name is Jean Hyatt. I am not being paid to be here, I have no association with any organizations. I got involved in this most important topic because my mother was diagnosed and you have heard her today, Audrey Borenstein. My mother was diagnosed several years ago with AMD and

now I see firsthand through my mom and many of her friends the devastation that happens to lives because of this loss of sight. I don't want to take your time to repeat what these other speakers have said in the way that it takes away people's independence. Just in my mom's case, she used to play tennis, go out, drive. Now she's pretty much house bound and I have seen a great effect on her emotionally from this.

Let me just say that I have read Dr. Bressler's report. It seems to me that these reputable doctors and organizations are doing this treatment and it's not experimental. From what I understand, and I have read and reread the report, it seems to be that while the results were significant, the criticism from Medicare was if the sample had been bigger, perhaps the results would have been different. That's kind of what I read. I see someone shaking their head. I can only say that the only thing worse than losing your sight is losing your sight unnecessarily, and what's worse than losing your sight unnecessarily is losing it because as a person on a fixed income who has paid taxes for 50 years or more, you don't have the $10,000 or so it would take for these treatments, and the government

decides that, quote, "It's not medically necessary," because that is the phrase written on the denials. So I pray that you will reconsider what you've heard and decide to cover this because it's the right thing to do. And financially, I think in the long run it would save some money in keeping people productive, happy, healthy citizens. Thanks for your time.

DR. DAVIS: Thank you. I just want everybody in the audience perhaps who isn't aware of this, to be aware that this committee makes a recommendation to CMS and it's ultimately up to CMS to make a decision on coverage. Thank you.

MR. CLAYPOOL: Hello. My name is Henry Claypool, and I am the co-director of Advancing Independence and Modernizing Medicare and Medicaid, a small group of people that are focused on what I have just mentioned. I don't hold any financial interests and in fact pumped my own gas, I paid for my own gas and then I proceeded to drive myself here, so I have gone out of my way to make sure that I can at least make this one point to you today.

It's critically important that the Medicare program begin to examine what the costs are around preserving the independence of its beneficiaries. In the case that you're looking at

today, it appears to me that if the agency persists in withholding treatment from individuals, it not only will result in blindness for those individuals, but it sends them headlong into a life of basically poverty as they spend down their resources to qualify for a health insurance program like the Medicaid program after they've lost their sight and become reliant on other federally subsidized programs to provide support to help them continue to live in their communities.

So again, understanding the panel is going to examine the science, and my support for the Agency is consistent. I was a former advisor to the previous administrator on disability policy and I hope that the science and the Agency can line up and support the independence of individuals in the future, and discourage the dependency that a decision withholding this treatment will create. Thanks.

DR. DAVIS: Thank you. Next please.

MR. JALBERT: I am Russell Jalbert, spouse of Lois Jalbert, who spoke earlier, and I'm here funded by QLT to accompany my wife, who needs help in travel. I am retired. I spent about 50 years, maybe more now, in business, in universities, in government, in nonprofit organizations trying to deal

with the issues of quality of life. In the government and universities I operated at fairly high level. In the other organizations I worked at the grass roots, where I still work. I work for mental hospitals, for rehabilitation centers, for visiting nurses associations, and I just want to make one point. That you consider the cost of nontreatment on this issue.

You've heard enough from other people to appreciate the effect on individuals and families. I think you should think also of the effect on larger societies. I'm a member of the Retired Executive Service Corps, for example, and there are tens of thousands of volunteers like me, older volunteers, and they, everyone of us who suffers this illness, and I am fortunate not to be one of them, diminishes the volunteer effort that is so essential to the benefit both to our neighbors and to our community and to our whole nation. So in your deliberations, I trust you will take into account the serious costs of not providing this treatment. Thank you.

DR. DAVIS: Thank you.

DR. BAGLEY: Good morning, almost afternoon. My name is Grant Bagley. I am currently an attorney focusing on health care and health care

policy issues. In that capacity I do represent Novartis and QLT. I've also represented and assisted a number of the beneficiary organizations that you have heard here today in seeking at least a review and a reconsideration of the evidence around verteporfin.

But I have another conflict of interest too, and that is that I was present at the very beginning in the formation of the Medicare Coverage Advisory Committee. Actually, before I was a health care attorney I was an obstetrician, and I will say it's one of the more difficult deliveries I have ever participated in. But I was present at the formation of that, and that's my other conflict. I feel passionately that the Medicare program is a wonderful program and it needs care and feeding, and that probably the most important thing in the Medicare program is that the Medicare program can move forward and start to make its coverage policy based on evidence. Evidence and scientific thought is what needs to drive our Medicare program, and an awful lot of what you've heard today could distract from those issues.

As Dr. Davis properly pointed out, this committee is here to evaluate the scientific

evidence, not make a coverage decision, not reform Medicare, not make social policy, but to talk about the evidence for this. I think we heard good presentations although because of time, we're very limited this morning, but you had good presentations, you've been given some information ahead of time, and I would urge and I will look forward to listening to a thorough discussion and an evaluation of the evidence so that you can vote on the question before you.

Now in terms of the evidence, the statistical inferences that can be brought from the studies that were presented, I think you got a good overview, you have all seen it, and Dr. Goodman is thoroughly familiar with the information because Dr. Goodman has gone over the data from these studies before, and assisted CMS in doing that. So, I think as the panel has its discussion, you have a resource which can help you through the data.

A new issue was raised in this panel hearing which wasn't raised before, and that was criticism of the methodology, and I think CMS had indicated the methodology was sound. Certainly FDA has been happy. The methodology has never really been an issue, and in fact you heard about two

pipeline products which are coming down the line, and they alluded to early Phase I and Phase II studies, and you heard the same end points, the same study design, the same kind of characteristics that are useful for this disease. I would simply urge you that if methodology becomes a concern in your deliberations this afternoon, while you do have a panel member who is knowledgeable about the data points, if methodology questions come up, Dr. Lee Jampole, who was the chairman of the independent data safety monitoring committee is in the audience, and should the need arise, I would urge you to use that as a resource if you do have methodology questions and they actually arise.

I look forward to the discussion, I think issues of economics are important, if there is time I would be interested in the committee's opinion, but the question before you is evidence and at least showing the Agency how to evaluate evidence and convincing the public that evidence is the way we should practice medicine and give guidance to our Medicare program. So, I look forward to deliberations. Thank you.

DR. DAVIS: Thank you.

DR. DOWLING: Good afternoon. Thank you

for this opportunity to make a few comments. With respect to your questionnaire, I have no financial interests from any source other than my own paying for a portion of my care. I have not served on any of the advisory committees or any other related organizations with respect to this particular problem. And from the last speaker, we heard that your primary reason for being here is the scientific basis for allowing this kind of procedure to be offered.

My name is John Dowling. I am a retired physician and before retiring I was Commissioner of Health in Nassau County, New York for 18 years. So I have some personal and professional experience with not only the scientific reasons for providing care but also the social impacts that attend the provision of care and also when care is not provided, and it's that latter point that I would like to address in my comments.

I am now an individual also who was diagnosed with dry in March of 2002 and in March of 2003 I was diagnosed with wet macular degeneration in both eyes, and I have had treatments in both eyes, and I firmly believe that without the treatment, I would now be functionally blind. At least I am now

able to remain very independent and go about my daily life. One of the things that happens when you are not able to, you go to other sources in the community for your support services. And based again as I said, my own experiences, the kind of support services you go to are the voluntary, public or community agencies that provide such in our communities throughout the country.

For example, if I were not able to drive or not able to do shopping, I would go to either a visiting nurse association or a government agency, or probably end up with a community agency such as Catholic Charities, who offer, among many other voluntary agencies, the kind of support services I'm talking about. And when you get to that stage, you would need a personal care aide who is going to cost you $15 an hour, or cost the Agency $15 an hour, or a home health aide if you also need some nursing care in addition to meeting your personal needs, and they run $18 an hour.

One of the things I didn't see in any of the information that's available, what is the cost, as a previous speaker had mentioned, of not providing this care. And not only that, but the ability of most of the communities around the country with

regard to the accessibility and availability, it's in extremely short supply. So if one because of the lack of this particular treatment, which as you heard from many of the previous speakers, many people cannot afford, they are placed in the position of becoming functionally blind and having to depend upon others to remain independent and not become dependent. When they then turn to the community agencies for assistance, when it is there, it is usually there in very short supply.

So my point on that aspect is in addition, I know that's not your province, but I would like to have it in the record because I think it is a topic that the federal and state government must address in saying that not only that we make this treatment, and personally I strongly support that this treatment be covered by Medicare, and when it is not available, that they also look into the other side of the coin and what we must do to strengthen our public health and other voluntary health services at the community level. I thank you very much for your time and attention.

DR. DAVIS: Thank you, and let me express my appreciation and the appreciation on behalf of the committee to all those who took the trouble to

present to us your views and going through the time and the difficulty to come here today representing the public, if you will, and certainly many of those who are affected by blindness or vision impairment. It's about 20 after 12 on my watch, and I think what we need to do now is take a quick and a somewhat abbreviated lunch break and then after lunch come back and proceed with questions from members of the committee to the presenters, including presenters from CMS and presenters from the requestor, and then move on with the rest of the agenda. There is a buffet that is available for everyone who is here, as I understand it, at McKenna's, is that the name of the restaurant here in the hotel? And I apologize that this is going to be rushed, but otherwise we will run out of time and not get to the important questions and votes at the end of the day. We will try and reconvene by one o'clock, so we will stand in recess until then.

(Luncheon recess.)

DR. DAVIS: Good afternoon. We're going to reconvene momentarily, and we'll proceed with questions for the presenters. I anticipate that members of the committee will want to direct any questions that they have in particular to presenters

from CMS or presenters from the requestor, and I hope all of them are available to answer any questions that we might have. And so, I'll just open it up to any members of the committee to pose any question that they would like, and you can specify who you would like to your answer. But certainly if there is a question directed to CMS that CMS answers and if somebody else has a burning response, you know, feel free to raise your hand and we will try and accommodate that. When answers are given to the questions, if you could please do that at the microphone, it will be easier for us to record it.

Yes, Steve.

DR. GOODMAN: I have a few questions. Probably Dr. Bressler might be the best one to answer this, but he can decide. It's all about the natural history. I'm a little unclear, there were differing statements made about whether all patients with this disease -- I'll ask the two or three questions all together and you can sort it out. Whether all patients with the disease ultimately progress to blindness, or at least legal blindness. In one case it was said that it burned out after a few years and stabilized at whatever point it was, and other statements were made that everybody would basically

go blind if untreated.
The other question, which is closely related, is how many patients with occult disease proceed to blindness without the appearance of a classic lesion at any time during their course. That is, are those who do progress, do they always go through classic or not, and the people who don't go to classic, does that represent an arrested form or can they proceed with the same degree of visual loss? Those are the two main questions right now.
DR. BRESSLER: So the first question, does everyone go blind, the answer is definitely not, so even with predominantly classic lesions, a large proportion will unfortunately drop to the 20/200 or worse level, if what's that's what you're going to consider it, but it won't be everyone. And looking at six-line loss or greater, that's when we say if you started at 20/50, how many go to 20/200 or worse, not everyone. And so I think it's reflected in each of the papers, whether you look at the change in visual acuity or the absolute level of visual acuity, not everyone goes blind from this. A majority do, but certainly there are people who remain stable when they walk in to you.
So it's a stuttering sort of thing. Some

people have lost vision and they walk in to see the ophthalmologist and it's stable thereafter. Other people stuttering, losing vision, they come to the ophthalmologist, they keep losing vision, then it stops, then they may lose vision again. But it appears by about somewhere in that one to two-year time period, most of the damage is going to occur if it's going to occur. There are always exceptions, so that some people that we follow for two, three or four years that remain stable, then suddenly drop further. That was the first one.

DR. REDBERG: There is no reliable predictor for who is going to go blind and who will stabilize?

DR. BRESSLER: No strong reliable predictors that we can say. It's more likely if, you know, if you are predominantly classic. It's more likely if you have a small lesion when you walk in with relatively good vision that you're going to deteriorate. If you walk in with a large lesion and you didn't lose a lot of vision, you're sort of a survivor. If you walk in with a large lesion and you already lost a lot of vision, it's not likely that you're going to lose more. So, both the lesion composition and independent of that the lesion size,

and independent of that the initial visual acuity walk-in probably affects the proportion. It's not everyone, it's a large majority, okay? And certainly the way one eye works doesn't predict the other, but we know if you get this in one eye, you have about a 50 percent chance of having the neovascular form in the other eye over five years, so this is a big problem, because the average age of 75 in the United States actuarial tables say if you make it to 75, you're going to make it to 85, so half of our people that walk in with the first eye affected within five years have the other eye affected.

Getting to the second question, does occult always go through a classic phase before it loses vision, definitely not. What can happen is you can have an occult lesion that slowly grows, destroys more photoreceptors, fully grows again, destroys more photoreceptors, and finally you have lost a lot of vision, and it may never develop a classic component. It could develop scar tissue that will have a bright area of fluorescence that could look like a classic component, but definitely they don't go through this process of occult to classic to vision loss.

There are some with occult that go through

a classic. We looked at the natural history. This is not published yet but we presented it at our Retina Society meetings. We looked at the natural history of the occult with no classic lesions in the VIP trial that developed classic and we said well, what do they look like when they develop classic? Now we didn't examine them at every time point, so we only had the month 12 and month 24, and when we pulled those in, almost all of them were so large at that point or had lost a lot of vision, or both, that they didn't meet the criteria in terms of vision or lesion size that we would consider treating them. So another reason we don't want to necessarily wait for occult lesions to become predominantly classic is because even if some of them do, that's just one component. Their lesion composition may become predominantly classic, but they may have already lost a lot of vision by the time that happened or already become so large that there isn't much vision to save.

DR. CURTIS: I have a question. The difference between the classic and the occult is made by the fluorescein angiography, you look at it.

DR. BRESSLER: Only.

DR. CURTIS: Right.

DR. BRESSLER: It's a pattern of

fluorescence.
DR. CURTIS: Right. So, is there any reason to think that these two processes are different pathophysiologically?
DR. BRESSLER: Not to any significant degree. So when we look histopathologically, if somebody surgically removes this and we look under the microscope, it is all fiber vascular tissue. So there is something unknown so far, we're just not smart enough yet, maybe we'll know in a few years as to what makes that classic appearance. It's probably a multitude of features, the amount of fluid that's there to allow the fluorescein to leak, the permeability of the vessels, the amount of scar tissue that's there, whether it's proliferating about the pigment epithelial layer or below. Each of these have been suggested, none are absolutes from information that we had.
But it does seem true that if you have this classic component, you might walk in at an earlier time point to the physician, because just a little classic brings a lot of vision loss and it brings the person in right away, and that's why a lot of our predominantly classic lesions were relatively small, whereas our occult lesions were much more

heterogeneous. Some were small, some were large, and that's why it was interesting that we seemed to see an effect of these smaller lesions, and that may be why the benefit was mainly driven by the smaller lesions in the occult with no classic, and in the predominantly classic, most of them were small anyway.

DR. CURTIS: And out of all the patients who have -- I mean, we're talking about patients with wet AMD and this is the 10 percent, right?

DR. BRESSLER: Well, 10 percent of eight million that are walking in there with let's say just oozing, or in a symptomatic intermediate stage, right.

DR. CURTIS: But out of this group, just for our information, about what proportion of the patients have classic versus occult only versus a mixed picture?

DR. BRESSLER: We don't know because all of our epidemiologic studies have been based on just a simple photograph of the back of the eye and this is determined by angiography, which we have never done in population based studies. And until these trials came out, we didn't have a reason to want to know from a public health standpoint, now we would

like to know. So I can only give you some rough guesstimates and we would suspect that about half of the people out there at least are occult with no classic. However, not all those have presumed reasons for disease progression, because remember, we took a select group that we thought were deteriorating when they walked in to the VIP trial, and that may be half of all the occult with no classic.

DR. DAVIS: Well, let me ask members of the committee to just signal to me if you have a question, and then I will try to keep track of the order. So Rita and then Wade.

DR. REDBERG: A few questions. One is, do you have any data on the inter and intraobservability of fluorescein angiography?

DR. BRESSLER: You mean in the interpretation of this? We do have data on the inter and intraobservability of the graders that did this information. As a matter of fact, just coincidentally, it's published this month in the September Archives of Ophthalmology. The Kappas are quite high for doing this information. They range around the .6 to .8 level for most of these features, is there classic, is it large, is it predominantly

classic. However, there also is information that there is tremendous variability among ophthalmologists, so it's one thing to have trained graders and the data you are being presented I think would be interpreted fairly similarly if we did it again and again and again, but among ophthalmologists, this is first of all relatively new, where to interpret occult neovascularization. As Dr. Wilkinson implied, he said we only see what we have now been trained to see and we look at angiograms differently now perhaps than a decade ago, and so there is tremendous variability among ophthalmologists in recognizing this. And we as ophthalmologists, as was stated, have been trying to go very strongly in trying to train people as to what are the nuances of this interpretation, and this will be very important.

DR. REDBERG: I guess in the TAP trial it said 61 had no classic, so they wouldn't have actually gotten in. Is that because the ophthalmologist who initially made the assessment had a different interpretation than the central center?

DR. BRESSLER: That's right. So there may very well have been a little bright area of fluorescence that was due to scarring or pigment

epithelial atrophy, by one interpreter. And then a grader looking at that said no, you know, I don't think that's classic or I do think it's classic. So there is going to be this slight noise, and it should be, you know, 10, 20 percent of these things. It shouldn't be 40, 50 or 60 percent. Then I would start to question, does that person even know how to interpret these. But there is some variability that guess on in that.

DR. DAVIS: Wade.

DR. AUBRY: Dr. Wilkinson in his presentation made reference to limitations of fluorescein angiography, in particular dye and other matters filling the subretinal pigment epithelial space. And I wonder if you could comment on that in terms of not only the VIP study but also in terms of clinical practice, how big a factor is that?

DR. BRESSLER: Pat's not here. I think he was hypothesizing on why there are these two different patterns of fluorescence, and he was saying maybe some of it is where the fluorescein collects, and collecting beneath the pigment epithelium might account for some of the fluorescence not being as obvious. I think its effect on clinical practice is only that we recognize that choroidal

neovascularization at the least has these two patterns of fluorescence, and they seem to impact on how large a lesion is when somebody walks in, and perhaps on the treatment benefit or when the treatment benefit is seen.
DR. DAVIS: Karl.
DR. MATUSZEWSKI: Dr. Bressler, in terms of the demarcation of the categories, we have occult, we have classic on both sides, and then we sort of have a mix in the middle. Now classic you can go up to 50 percent or greater, but occult is 100 percent or else it's mixed?
DR. BRESSLER: Correct.
DR. MATUSZEWSKI: I don't understand that middle category.
DR. BRESSLER: The middle category, again in looking at this information, was that there is some classic neovascularization in that fluorescent pattern, but it doesn't occupy at least 50 percent of all of the abnormal area. So there is a total abnormal area, it could be classic neovascularization as part of that abnormal area, occult neovascularization as part of that abnormal area, some blood, perhaps some pigment. And the total abnormal area is one thing we look at, that's classic

and occult, why we need to recognize all of it, that's the total abnormal area. Then we say how much classic fluorescence is in that total abnormal area. More than 50 percent, we called it a predominantly classic. Zero classic is just occult, and maybe some blood and something else, we call it occult with no classic. Everything in between, we saw a little bit of classic or more classic but not 50 percent or more.

DR. MATUSZEWSKI: So 99 percent occult, 1 percent classic makes it a mix.

DR. BRESSLER: We called it minimally classic, if that happened to have come up. We had to draw the line somewhere for this investigation.

DR. MATUSZEWSKI: That's why I'm not sure in clinical practice and in clinical trials that why wouldn't the classification scheme be sort of third, third, third, rather than this occult has to be 100 percent, otherwise it's a mixed version, where as the classic has so much more room.

DR. BRESSLER: I think there are lots of ways that it could have been done, and because we were suspicious that any classic might rapidly grow in that area, we just drew the line between saying is there any classic or not and if there is some

classic, is it predominantly classic.
DR. MATUSZEWSKI: If you're a provider and you start with an occult lesion and you treat it, and then it turns into a mixed animal, would you at that point at the third month or sixth month stop treatment and say it's now a mixed animal, I'm not going to treat further?
DR. BRESSLER: We would not, and that's an excellent question, because what happens over time is scarring develops and atrophy of the retina develops, and it makes it harder and harder to pigeon hole the fluorescence patterns into classic or occult. They begin to just stain with scar, and you and I and people training in this couldn't begin to separate it anymore. So these described patterns of fluorescence, when a person is first becoming symptomatic of these lesions, or when it's not too large, or when things have just started. Over time, three months, a year, two years, for a clinician, we just try to determine, is it still leaking fluorescence but we no longer try to pigeon hole it into classic or occult neovascularization.
And so the situation you described, we would say okay, it was whatever pattern at baseline and now three months later it may have changed. If

three months later it was leaking fluorescein, regardless of what we thought the pattern was, because it gets harder and harder to define the pattern, then we would have recommended treatment.
DR. MATUSZEWSKI: So you treat the pattern, not necessarily the visual loss, visual assessment.
DR. BRESSLER: Now you're getting into what do we recommend as physicians based on this information. So if for example, someone has lost a tremendous amount of vision at follow-up, if from a quality of life standpoint we think losing any further vision would make no difference to that patient, and that's sort of a judgment you have to make on each individual patient, what's their other eye like, what are their needs, what are they doing, what do they express to you is going on. I could easily foresee, and it comes up all the time, where someone is still leaking and yet, we decide no longer to treat them because we fail to see why that would be any different than leaving them alone. There may have even been a guidelines article that we shared with you in the materials where we got people together to try and write out in detail these different situations of how we would

apply these results to the practice, and that's just one of them where if it gets so large with such large amount of vision loss that the person might not benefit from further treatment, just because it's leaking, we wouldn't recommend it. Now this is a judgment and it differs with each person, but it can be written, so to speak, for a provider to explain to a physician.

DR. MATUSZEWSKI: And just one more question to clarify. So again, if you start out occult and in three months you have some mixed lesions, mixed pattern, you would not treat with OPT. But if at six months you again were now 50 percent classic or greater, you would then consider again retreating with --

DR. BRESSLER: No, I apologize and I will just go back. If it starts with occult and I decided to treat it, then no matter what it looks like at three months, I might still consider treating it, because I no longer do this classification at follow-up. This is only applicable when the person walks in. If I followed them, if I didn't treat them, then of course they're untreated, and I might interpret that at follow-up.

DR. MATUSZEWSKI: So at the second

treatment you would continue to categorize it as an occult or a primary occult even though it no longer fits that categorization anymore?
DR. BRESSLER: Yes, and that's how the first Medicare coverage also was written, that the follow-up treatments are based on whatever the decision was when the person walked in and the course of therapy was being initiated. Rather than individual treatment, it was sort of we're initiating a course of therapy.
DR. MATUSZEWSKI: Okay.
DR. DAVIS: I have Linda, Bob, and then Barbara.
MS. BERGTHOLD: Given how complex the diagnosis of this and the categorization, the classification, and all of the things we've heard today, and this may not be a question that you can answer but I hope you can at least make a stab at it. I am concerned about thinking about something like this disseminating into the professional community and what the quality controls are. I totally trust you to make good decisions. You're well educated by this, this is your life, you do this all the time. But there are lots of doctors out there and we heard one today who said, you know, I told her to eat 79

vegetables or something. You know, there are lots of doctors out there who would not be able to diagnose adequately, who might not know when to treat and when not to, but it's covered and so they do, and so this causes harm actually. So what are your concerns and also, just another issue, that this reasonably competent physician does not inspire in me a lot of confidence. I want more than a reasonably competent, I want a highly competent physician as a standard of care for this. So what ideas do you have about quality control and quality assurance.

DR. BRESSLER: I think this is true of any condition that we're treating, where you can't just get, for example, a sodium value and make a decision on that. And so I think it's important that we work with our colleagues and be sure that they are interpreting this information in as uniform fashion as possible. One thing that we've learned from these trials is that it appears there may be some stronger benefit for relatively small lesions. And just recognizing, is the angiogram abnormal or not abnormal is a little easier than determining how much is classic and occult, et cetera.

So one thing that we're trying to push

people that may be a little easier, so whatever this confidence level is that you're trying to get to do is saying okay, well, it's a little easier to at least say is it normal or abnormal and then, you know, don't be so cavalier about treating something very large, but very small regardless of the lesion composition, I'm pretty comfortable that we have some benefit here.

But your point gets to, we only just learned this information two years ago, and I think we do have to create systems that will do better education, that will allow people to be more confident in dealing with the information. The spinach thing, or giving lots of vitamins or something, also is critical. There was a study only shown a year ago, two years ago, about certain doses of vitamins and minerals reducing the chance of this neovascular form from developing the first place. Nice government study and yet, I can tell you right now, not trying to interpret angiograms, there are plenty of physicians who are mixing up what they're supposed to tell the people based on that. So you're getting to I think an important issue and this is just one example of it, and I think we have to do everything we can to educate them.

DR. DAVIS: Bob.
DR. BROOK: If I'm hearing you right, let me talk about this for the average Medicare person being treated in this country or will be treated in this county. Right now, it's reimbursed for classical lesions. Classical lesions seem to become, affect vision much quicker or make a change in vision quicker, brining people to the doctor earlier, maybe not earlier in the course, but earlier in terms of the size of the lesion, so you see predominantly small lesions. Occult lesions seem to be, and correct me if I'm wrong, occult lesions seem to have a slower course or change vision slower, so that the patient is not aware of this and basically by the time they get their eye exam or somebody pays attention to this, whoever it is, their lesion is much bigger on average. Is that basically a correct statement?
DR. BRESSLER: I would revise it in just one slight way and that is, the occult lesions are more heterogeneous, so some of them walk in just like those predominantly classic lesions, so that they are small and they are very symptomatic and they walk in, but others do indeed take a while for somebody to recognize, unfortunately, so they may walk in quite

large and with relatively good vision.
DR. BROOK: That would relate to the quality of their eye screening and all the other kind of stuff that's going on, but the fact of the matter is, this seems to define a subset of patients who, occult in general that makes, before people walk in for whatever reason or get diagnosed, that the lesion is bigger.
DR. BRESSLER: On average, right, because there are plenty of them who walk in with real tiny ones that were fortunate to capture.
DR. BROOK: So that's the first issue. The second issue is you said that it's very very difficult on average, among average people that are going to be doing this, to -- I mean, there's still some controversy of what's normal and abnormal on the fluorescein angiography, it's much much more difficult, so that this is going to slip back to anybody who has an abnormal angiogram and a small lesion ought to be studied is my sense of what you're talking about.
DR. BRESSLER: Anyone with an abnormal lesion that has been progressing recently --
DR. BROOK: But even progressing, you're not going to have two points of eye vision, you're

not going to be following people, you know, so --
DR. BRESSLER: You can.
DR. BROOK: But it sounds like you're going to be treating everybody.
DR. BRESSLER: No, no. You know, if you're not sure, come back in a month.
DR. BROOK: So let me ask your standard of care for progression then. Would that require a loss of a line, if you saw a small occult lesion, you would not treat that person unless you had in your records documents that their Snellen line chart had deteriorated?
DR. BRESSLER: Or whatever I am most confident at. So if I had a very competent physician from the outside with a very excellent vision of 20/25, and that person was documented on their photographs to have an occult with no classic lesion. And they come in to me and they are 20/50 and they say they're worse, yeah, I'm comfortable with their progression.
DR. BROOK: So you would insist on two objective measures?
DR. BRESSLER: For the occult with no classic, that's what we insisted on in the VIP trial.
DR. BROOK: I'm trying to understand what

you believe the evidence is. So at the moment you believe the evidence ought to be, if there is a Medicare evidence based rule, to say that there has to be documented objective change some way, either comparing two doctors, on a Snellen chart, with an occult lesion, to warrant treatment.
DR. BRESSLER: Or we had blood or we had documented growth of the lesion, and I think those were good guidelines.
DR. BROOK: Okay. So there has to be documentation, so you're not asking for coverage of all small occult lesions even.
DR. BRESSLER: I'm not, because in general, there are rare exceptions that I could think up for you, but in general I think they should mirror the cases that we enrolled in the trial because they deteriorate.
DR. BROOK: I understand that, so that's where you're coming from. I just want to find out where you're coming from. Now, in the data that the trial presented, I don't care whether it's before or after the fact, it seems to be, would you agree that the effect at one year was minimal at best?
DR. BRESSLER: Only for the three-line loss, but there are all different ways of cutting the

vision. For the six-line loss, for the average visual acuity loss, for the contrast sensitivity, I would say it was not minimal at best, it was modest at best.

DR. BROOK: I think the only one that was significant was the 20/200; is that correct?

DR. BRESSLER: And perhaps the six-line loss, and perhaps the mean visual acuity change as well.

DR. BROOK: So putting this together, there is a group of patients that get harmed by this procedure, and there could have been 13 people testifying in the public session that you did presumably, that wound up having permanent loss of vision.

DR. BRESSLER: Correct.

DR. BROOK: But they didn't come to this hearing to testify.

DR. BRESSLER: I'm happy to have them talk with you.

DR. BROOK: Well, you identified the patients, a lot of them are your patients, the ones that come seem to be happy. What I'm wondering about is you as an ophthalmologist, realizing that if they used just progressive criteria and it hadn't

progressed and it was occult, and it was small, that's the criterion that the evidence best supports in terms of doing this?
DR. BRESSLER: Yes.
DR. BROOK: Then you believe that the benefit at two years when used by the average ophthalmologist in this country would exceed the harm.
DR. BRESSLER: Yes. Because fortunately, the harm appears to be way outweighed by that benefit. Those cases of acute --
DR. BROOK: Let me ask you one other question. Are the people that are harmed, what proportion of that category would actually go on in your best clinical judgment to lose a lot of vision? And remember, you're harming some people that wouldn't progress.
DR. BRESSLER: Half of them, 50 percent.
DR. BROOK: So half the people you're harming would probably have not lost vision because we don't know enough about the natural history of this disease, if you had not treated them.
DR. BRESSLER: That's right, 50 percent of the 4 percent, or whatever.
DR. BROOK: Do you know of any better way

to get more benefit for less, given the evidence, is there any way to get more benefit?

DR. BRESSLER: Yes. It appears that the people that were harmed -- now we only have ten of them so we have to look in detail, and there's not a lot to look there, started with relatively large lesions with relatively good visual acuity. And personally right now, we avoid those except in a rare circumstance that I can tell you has happened, but in general, large lesions with good vision I probably avoid, and that might reduce that risk even further.

DR. DAVIS: Dr. Azab, I think you wanted to jump in here?

DR. AZAB: I just wanted to clarify a couple of things that may be of value.

DR. BROOK: Before you clarify, would you agree with everything that he just said? Where do you disagree with what he just said?

DR. AZAB: I am not disagreeing with anything.

DR. BROOK: So you agree with everything he just said?

DR. AZAB: I'm saying I wanted to add information about the severe visual acuity decrease in the patients with lost vision. The natural

history of this disease of course is the continuous loss of vision. Sometimes whether treated or not, there will be a lot of patients losing vision. The adverse event of harm, which is the definition of harm, is those 10 or 11 patients that had severe visual acuity decrease immediately after treatment within seven days, well, there is a temporal relationship, and that is I did here and I just wanted to clarify, this is in addition to what Dr. Bressler said. The visual acuity scores of the natural history, if you look at the natural history in the first year, they, left untreated the first year and the second year, and long-term, their vision on average is similar to those in the worst outcomes.

DR. BROOK: Can I ask you one other question and I'll shut up. Everyone has said that functional life was better. Why is not the primary outcome of this being function and what really happened? I mean the primary measure should be function, and I just don't understand why function wasn't there.

DR. BRESSLER: The ophthalmic community has not yet taken in an instrument of visual function to be stronger than visual acuity as a measurement, so that's why it wasn't, it just wasn't accepted yet.

These instruments are getting good and the information I showed you from the submacular surgery trials from the March Archives of Ophthalmology shows probably the three and six-line loss is unquestionably a reflection of function.

DR. REDBERG: The results that we were given said that you actually did visual function questions in the VIP trial but there was no difference between the treatment and placebo group in the function.

DR. BRESSLER: Yeah. As I understand it, those weren't done except in English, I could be wrong, because the instrument had not yet been validated in other languages and we did this all around. In addition, as I understand it, we would have to control those for whether it was the first or the second eye involved. Those instruments of visual function depend on your overall functioning, not just what the one eye is doing, so by the time we control for taking out the second eye and just the English speaking people, we don't have many cases to look for.

As it turns out, I don't know if Mohammad is here, the visual acuity also, in the people that participated in that visual function questionnaire,

ended up being a subpopulation that lost vision equally in the treated and placebo groups. In other words, that small subgroup that was pulled out had the same visual acuity amount, so you wouldn't expect them to be different.
DR. REDBERG: It says 85 percent of the people in the trial completed the visual function questionnaires.
DR. BRESSLER: Is that right? Then I'm going to ask Mohammad to comment on that, because I don't have enough information on the vision function then. I may have been thinking of the TAP trial.
DR. DAVIS: Dr. Azab.
DR. AZAB: What I tried to show is an indication of why the visual acuity loss of three lines, which is a moderate visual loss that we see, is actually an indicator of function. This is actually the health related quality of life data comparing between the patients who lost three lines or more, that's the nonresponders, and the patients who did not lose three lines, that's the responders. And you can see, this is whether or not they were treated, so this is not the treatment versus the nontreated, this is whether they had a three-line loss or not, which is the primary outcome. And you

can see here in all the visual function scores, a lot of them are significant, and in the overall score, it's highly significant. This was TAP and the next slide is VIP. You can see exactly the same thing, that the moderate vision loss, which is a primary end point that we were using in these trials, is highly correlated with the visual function scale, that the responders have a much better visual function, highly significant than the nonresponders, that's the three-line loss yes or not.

And the next slide, or the slide after that. The TAP trial quality of life data, there were very few patients, you are absolutely right. For the VIP trial where there were more patients, there was still fewer patients, there was not a representative sample of the patients who had a better seeing eye because we did not expect to have a health quality of life difference. We compared the overall sample of VIP which showed this difference, which is the benefit. So the overall sample of the VIP trial, that's the intent to treat analysis, showing a difference in favor of verteporfin of 13 percent, 17 percent, 18 percent, and the average scores were better in the overall trial for verteporfin by six

letters.
If you look at the patients, although they were a relatively large group of patients, 161, so about half the patients enrolled in the health related quality of life sample, if you look at their data, the difference between verteporfin and placebo in these patients who entered the sample of quality of life, the difference is much smaller and on average, their visual acuity score was actually almost identical. So the sample of the patients that filled the health related quality of life in VIP did not have the same benefit as the overall population, and that's why they didn't have a visual function benefit.
DR. REDBERG: Why does it say 85 percent of the patients with AMD in VIP trial failed the health quality of life, and you have data there for 161 out of 339?
DR. AZAB: These are the patients that filled out the questions at the beginning and at the end, and had a better seeing eye.
DR. REDBERG: Why did you eliminate all the other -- here it says most patients with AMD, this is your data, from the VIP trial completed both baseline and month 24 HQL assessments. But you've

taken, you're not showing us the 85 percent.
DR. AZAB: This is the patients who had the better seeing eye. In all the visual function practice, it means that the study eye was their second eye. The individual function in order to have an effect on the visual function, you have to have the better seeing eye as the study eye, that's been published, so this is the sample that had the better seeing eye.
DR. REDBERG: So you're saying the design of the trial, you didn't necessarily treat the better seeing eye in treatment?
DR. AZAB: Correct. Whether the patient had one eye or two eyes affected, there was always one study eye for each patient, so each patient had one eye of the two studied, not both eyes, and this eye could be the better seeing eye or not.
DR. REDBERG: So you're saying if you had treatment but not in the better seeing eye, you would not expect to see an improvement in functional quality of life.
DR. AZAB: That's right. That's already published.
DR. REDBERG: So the recommendation would be to only treat the better seeing eye, because you

wouldn't have an improvement in functional status if you were treating the other eye?

DR. AZAB: That applies to any therapy for vision.

DR. BRESSLER: I would always recommend treating the first eye, although I can't do that sort of analysis when it's the first eye, because you never know how badly the second eye is going to end up. And since 50 percent of them within five years, when most of them will still be living, are likely to have their second eye involved, we want to try and maximize the most vision we can for them.

Now, you also do get some benefit when that second eye is involved from wherever your first eye is, but you can't go backwards five years and say okay, now I will go treat that first eye. So we always consider treating the first eye, even though it's not likely to have a big impact on their quality of life then, because it's likely to have an impact on their quality of life in the 50 percent where the second eye gets involved, and I don't know who to predict that's going to happen to yet.

DR. DAVIS: Dr. Stone, did you want to comment on this particular issue?

DR. STONE: Although there's initially an

appearance of something antagonistic about our side and their side, I want to make a comment about this that I don't think quite goes that way and that is, it's important to note that this is an efficacy trial and not an effectiveness trial, that it is interested in judging the impact of the drug, which is a primary concern of the FDA and done for licensing, and as such, it's difficult to draw conclusions about overall effectiveness and function. And in some ways looking at those, you can't get the same functional information you would like. It's as if from the start, you would have done an effectiveness trial and said we're only interested in how this is going to look in the real world. So we don't care what the Wilmer Institute fluorescein angiogram interpreters feel that these look like. In the real world people aren't going to be doing this, in the real world doctors of all sorts of quality and philosophy will be performing this procedure and will be treating one eye or both eyes, and those eyes won't matter. And of course if you do it that way, you create a lot of noise about the efficacy of the drug itself, whether it is better than placebo, whether it really works or whether it's snake oil. And again, you have to really make two different kinds of trials

to answer those two types of questions.
DR. DAVIS: I have Barbara, Oliver and Margaret on my list. Barbara.
DR. McNEIL: This is for Dr. Bressler. I must say, I read this material I though extremely carefully before I came. I was very confused when I came in. I was grateful for a lot of the clarifications actually that came from the requestors. I still don't have this fully in my brain as to what the right thing to do is. One of the things that bothered me the most about this was the fact that I was having a lot of trouble keeping track of confounders related to the definition of the disease, the occult to the fully classical, the size of the lesion, and the level of baseline visual acuity. And it seems when one of them got included or didn't include, the results changed depending upon whether you were looking at the whole cohort as in the TAP trial, versus subgroups when you controlled for changes in visual acuity. So those three variables seemed to play a big role in what the final results were, depending upon the whole cohort and the subcohort.
So my question to you is the following:
Is there any merit of rethinking the definition of

this disease entirely and basing it upon size and then controlling for these other things, rather than in this somewhat, what I perceive as an artificial distinctions of 100, 50 to 100, and zero to 50, I guess?

DR. BRESSLER: I think on the top level there is merit in first approaching it from the lesion size. From the retina specialist's point of view in discussing and thinking about each person, while we would want to err towards treating smaller lesions, these confounders do appear to impact the results so that if it were a predominantly classic lesion, even though it were somewhat large, I would err more towards wanting to treat that. So it adds to, the top level I think should be lesion size, as you said, but I wouldn't want to throw out everything about lesion composition yet.

DR. McNEIL: So I guess the follow-up question if I can, Ron, on that, are there data to support what you just said, or is that an intuitive feeling of yours?

DR. BRESSLER: There are data to support that and this was in some of the analyses that are in the September 2003 American Journal of Ophthalmology.

DR. McNEIL: So we haven't really had a

chance to digest those; is that right?
DR. BRESSLER: Correct, not in detail.
And I will just point out one other thing that George Williams from the Academy had mentioned when I was sitting on the sidelines there, and that was in terms of interpreting these things, the recommendation in the ophthalmic community is not that this go to every single ophthalmologist or any eye care provider. It is recommended and written down by the Academy, by our guidelines that we've written, that this go to the retina specialist who's familiar with angiography, who's doing this. And even then it may be difficult, but we are trying to limit it in that way. Now who is a retina specialist? There is no defined term, it's not a board certified specialty, but we indicated that it's someone who is familiar, comfortable and able to interpret angiography and look at the retina as well. So I wanted to add that. If we're going to ask for lesion size, you can't throw out all the difficulties of understanding what is classic and what's occult, because to know the size, you have to recognize all the classic and all the occult. But it is harder, as you said, to look for, is it 75 percent classic or is it 50 percent classic? So I would

agree with you. Now what we've learned over time is I would start with the lesion size.

DR. McNEIL: Do you think that this committee would have an easier time dealing with this mound of data, both the data that were received in our six-inch stack as well as what was presented by all of you this morning, that we would have an easier time dealing with the conclusions had the top level been defined differently?

DR. BRESSLER: Now in retrospect, yes. We have a much better understanding of this condition. I'm sure we will continue to learn, but I think if you had started with all of the lesions that we entered in TAP and VIP trials which were fairly similarly handled, and you looked at just all the smaller lesions, you'd see a benefit. And if you looked at the larger lesions, there would be a much smaller benefit of putting them all together. And then if you in fact dissected that, you'd see that that much smaller benefit was really only driven by the classic containing lesions that happened to have been large.

DR. DAVIS: Oliver.

DR. SCHEIN: I have actually much less to say now that Dr. McNeil hit the point right on the

head that I was trying to make. I think we are in this ironic peculiar situation now because of historical things that have happened with the demands and requirements of the FDA for certain kinds of efficacy trials where a priore it was the clinical expertise that classic lesions both progressed more quickly and might be more amenable to treatment; therefore, more effective for a drug company to look at that first. You then end up with a restriction based on angiographic criteria.

And to get to points that have been made earlier, Neil and I have done some projects together over the last two years where we can tell you the rates of inaccurate designation of predominantly classic by retinal specialists in practice in various locations in the country, which ranges from 20 to 40 percent, so very very high. These are not general ophthalmologists, these are retinal specialists. So, there is already an inability to recognize lesion type on a reliable basis.

The data which is, you keep referring to coming out this month, is I think the most germane data of all, which shows that size and recency are very important and probably much more important than these distinctions, which will only become more

difficult to make from a policy perspective rather than an individual patient perspective. Now you have approval for this group but not this, you're going to add on another group which really overlaps the first group midway through a treatment cycle.
So I wanted to get your input and raise for the committee the possibility of recommending approval on a completely different basis and not based on the rigid FDA criteria. In other words, try size and recency, and perhaps initial acuity.
DR. BRESSLER: Again, this is looking for approval of a physician's judgment from the totality of the data that they look at, not approval to market a drug under a certain label. And I would say, in looking for approval of a physician's judgment, that the best information we have now learned, and you want coverage policies to be elastic to what we learn, is to consider that the lesion size is important.
These have to be written, though, as guidelines, because the same problem we ran into with the predominantly classic, you run into a little bit with the lesion size, but I would agree with you as I have said earlier, that that doesn't necessarily mean that every case we're treating is an FDA approved

one, because the FDA approved it for predominantly classic, and maybe they would have done it differently had we had this information differently, but their rules are different that they go by. So I would agree with you that if coverage was for, you know, some lesions that happen to be small regardless of whether they're predominantly classic, that gets to what physicians are recommending right now, what the Academy is recommending, what the retina specialists are recommending.

DR. DAVIS: I have Margaret, Alan, Paul, and then Steve and Wade, and then at that point, we might need to start going back to the agenda. And of course when we start looking at voting questions, we can discuss those, and if there are questions specific to a voting question, then we can, I suppose come back to some more discussion. Margaret.

DR. PIPER: Thank you. Two items. The first is a follow-up to the discussion of functional quality of life assessment. Understanding everything that has been said so far, I'm still curious. This was a prespecified secondary outcome that doesn't seem to have gotten the same degree of attention as other secondary outcomes, even though I think we

agree that it's an important kind of outcome to assess. I understand the need to look at the patients in whom the treated eye is the best functioning eye.
Looking at that subset, though, I'm not sure that the fact that the benefit wasn't as great in that subset is the only reason to say that therefore, they are not representative. So for example, was there any analysis done of baseline characteristics of that subset in relation to the rest of the population?
DR. BRESSLER: Not that I'm aware of, but Mohammad may know otherwise. I just don't think it was looked in more detail, because I think we knew from the start that we were inadequately powered to look in detail at these quality of life outcomes because we knew that would only deal with the second eye, and so that these were in fact to collect some information to learn about it if we could learn about it, and I think the most we've learned from it is that visual acuity loss does travel with vision function loss. I think three and six lines is not just a little noise, I think they're pretty accurate.
And I think if we did have, balance a baseline for these features, if we did have all second eyes that

were involved, it's extremely likely that we would have shown consistency among those.
DR. PIPER: Well, I was glad to see the data that seems to validate this as a measure, or at least take a few steps in that direction, and that's what made me all the more interested to know more about that subset and why are they, you know, are they representative of the population or are they not in any other way, so that might be interesting to look at.
My second issue is methodologic and I may have just missed this in the CMS and requestor analysis. I was wondering if the significance analyses of the secondary variables were corrected for multiple outcomes.
DR. BRESSLER: I don't think so as far as I understand, but I'd have to ask the statistician. They were not corrected for multiple outcomes?
DR. AZAB: We actually specified in the protocol and the primary analysis plan that we have one primary efficacy variable, which is a primary outcome of 15 letter loss at 12 months. We didn't correct for the secondary variables. But having said that, we in terms of the corrections for the secondary variables, the levels of significance that

we have seen here even with multiple corrections since we have calculated out to 23 corrections, dividing the .05 by 23, these P values, some of them will still be significant.

DR. PIPER: Do you have any data to show that?

DR. AZAB: Yeah, we do.

DR. PIPER: I mean, so you have done some of the corrections?

DR. AZAB: I mean, it's not appropriate to do post hoc corrections, but we did post hoc corrections to see whether these P values will still stand as significant, and some of them are, and we can look at those.

This is, the most conservative correction is just to divide by the number of analyses, which is the most conservative method. Actually this will be really conservative here because most of the vision loss levels are not independent, they are dependent of each other, and also the 12 months and 24 months could be dependent on each other, so this will be really extremely conservative. But even if you take that, we've calculated with the ten end points, the one primary and the nine secondary efficacy variables that were set, analyze for the ITT data set at 12

months and 24 months, that's 20 tests. And we calculate here for 23, because in one of the evaluation reports we had also some VM data so that was the number, 23.

If you divide by 23 the .05, then your significant level, .002, that will be, if you have any tests at .002, because once you correct, then any test will declare significance, because once you take that correction, it means that you just need one of them, of these 23 to be that .002 or less to be significant.

And if you look at the data, next slide, this is the data once again from the primary data set, which is the intent to treat data set. This is all patients, there is no exclusions. Looking at the three lines, six lines, the level of legal blindness and the mean visual acuity decrease. You can see these are the red P values. That six lines, which is the severe vision loss, this is actually reported the other way around, the patients who did not lose six lines, it's the same thing, and the patients who lost less than 20/200, both come at the .001 level so actually below the .002 required, even if you take the full adjustment values.

DR. PIPER: Thank you. Dr. Stone, did you

have any comment?
DR. STONE: Well, one of the questions is of course, how do we know the number is 23 and which again, goes back into some judgment because as Dr. Azab said quite properly, you are doing this in a post hoc way. There was nothing in the initial analysis plan to say we're going to look at all things and make the adjustment for 23. In fact, that was particularly the problem in the TAP trial when there were specifically eight outcome variables and they made no acknowledgment, eight primary outcome variables.
So it is tricky. And then you know, which of those, is 23 really the core group, because you're excluding things that because they're post hoc don't seem to be of any interest, and so it's very very tricky when you go that way.
If you start out from the beginning saying there are lots of ways that a significant result could be reflected, we're going to identify 10 of them, therefore our significance level is going to be .005, no problem.
DR. GOODMAN: Can I just follow up directly on that?
DR. DAVIS: Yes, Steve, and then we'll get

back to Alan.
DR. GOODMAN: I just wanted to ask you, what would be other ways that they could have done the analysis that they ignored? And it seems like most of these are different ways of looking at survival curves or averages. I'm having difficulty figuring out among these many other analyses which are the ones that would be central to the conclusion that they might have ignored and selectively focused on these, which do seem to be, aside from the quality of life and functional issue the standard ones that are used.
DR. STONE: Well certainly as an example, quality of life is one. Also, again, the division into subgroups, we might have some information that for example, it works better in men than in women, or in a different age range or in a different starting point in visual acuity. You know, we already talked something about lesion size.
DR. GOODMAN: So it's the subgroups that you're really concerned about.
DR. STONE: Yes, and actually there are a number of other -- I can't think off the top of my head how many -- well, the subgroup, occult itself is a subgroup, and how that was defined and whether you

can bring in other lesion components, you're going to have to just split it into occult and classic, so there is a variety of things that are going on. And in fact, I think in the initial TAP protocol when they said we don't really know how this is going to show up so we are going to pick out eight different ways to look at this, if they had done that with some adjustments, then it would have been very straightforward, but again, it just wasn't looked at.

DR. DAVIS: Bob had a specific follow-up, and then we'll go to Alan. This is related, Bob, is that right?

DR. BROOK: Yeah. You made a lot of critiques about the methods and the analysis, which are sort of standard book critiques about what you can do with analyses. I'm going to give you macular degeneration with an occult lesion and the data set. Do you want to be treated? I want you to address the question of, you have now seen the data. I want you to conclude -- I mean, you gave us a theoretical discussion and you don't have to answer it that way, but you gave us a theoretical discussion of all the things wrong with the study. There is not a single study that we can't find a lot of things wrong with. But you heard the following things which I

think we have to believe from the ophthalmologists. They don't know how to distinguish between small occult lesions that are going to go on and cause blindness and those that aren't, they think it's about 50 percent. They don't really know how to diagnose very well occult versus classic lesions, they don't even know how to classify them very well. They did randomize these things. They seem to have followed up a reasonable proportion of the patients. They made reasonable efforts at all these activities, and at three years -- and they can't do anything in the middle of two years to distinguish which ones to treat or not. I mean, that's what I have heard. This is a rudimentary science. You've got 39 countries that have looked at this data and who have said they would cover it. If you have a small occult lesion and walked in the door, given this level of uncertainty and your analysis, would you want to be treated?

DR. DAVIS: Dr. Stone, could you just hold off on answering that? I really don't think that's a direct follow-up to the questions that we were posing before. And if you want to answer that, you can come back. I would prefer to continue on.

DR. BROOK: I apologize, I thought it was

a follow-up.
DR. DAVIS: Well, I would prefer to continue on. I'm not sure I even feel comfortable asking a CMS analyst to personalize this in that way, but if the rest of the committee wants to hear that answer, then we'll ask if he'd like to answer it.
Alan.
DR. GARBER: This is a question for Dr. Azab. You mentioned very briefly and I didn't catch the details in your presentation, which by the way, I found very informative and helpful and really appreciate it. But you mentioned very briefly that you are about to start or you just started a trial for FDA approval. I didn't catch the details but I think it's for occult or predominantly occult, or occult without classic. I was just wondering if you could tell us a little bit about more about the trial, what the prospective hypotheses are that you're looking at in this trial, what the patient population is like, and I assume it's a randomized controlled clinical trial, so if you could just give us some brief comments about what that trial will be addressing and how it's designed.
DR. AZAB: I will be happy to. I just wanted to make a correction. There are several

statements made about TAP and we have eight primary outcomes, we didn't choose them correctly. TAP is approved worldwide and FDA approved, and in the protocol there were four analyses at 12 months and 24 months, that's correct in the protocol. In the original analysis plan that was approved by the FDA before unmasking, we chose one of them in discussion with the FDA, and that's why we didn't make a correction. I think Dr. Stone didn't have access to the original analysis plan, that's why he's making the comment on the protocol.

But for, I'm delighted to give you more information about the other trial. When we discussed with the FDA and they required we do a second confirmatory trial on the occult to comply with the guidelines of having two adequate and well controlled studies for this indication, we started the study a little bit over a year ago. This study is now well underway, it is completing enrollment, but we have to remember as we are completing enrollment as we speak, there will be at least one year follow-up.

By the way, on the methodology of the trial, which also, the protocol as approved by the FDA is identical to the VIP trial. The only thing that is different is that we have now taken the

outcomes of one year and two years as primary, and made an adjustment. So we made adjustments for the multiple analysis, that's the only difference. But otherwise, masking and all the methodology of the new trial is exactly the same. It is randomized, placebo controlled. The patient population are occult with no classic lesions who have less than six disk areas. So since the VIM trial, which as you've seen here from Dr. Bressler is less than six disk areas, we have now almost amended most of our protocols to make sure that we get the benefit in the patients treated in a clinical study to less than six disk areas. That is because we are still studying occult and minimally classically where the lesion size matters. We do have a lot of lesion size analysis in predominantly classic and in this population lesion size doesn't matter.

And maybe going back to Dr. McNeil, that's why probably having the top line as lesion size, and I think I agree with everything that was said, but the only problem with that is actually the lesion size factor, confounding factor doesn't really apply to the predominantly classic population, because predominantly classic really benefits no matter what lesion size is.

DR. PIPER: Are you assessing function in that trial?

DR. AZAB: There is no quality of life assessment in this trial. One of the reason we had few patients, we really did hope that we would get good quality of life, but two reasons. We didn't have any criteria to have better seeing eye in the study. The study eye of the patient could be the first eye or the second eye, so we really didn't get -- and you see TAP was very little, VIP was more, but still not enough, so we're not adequately powered to really detect differences in the quality of life. The other thing is that we had to limit it to a sample because the VFQs, or at least at the time was only validated in English, so we had to speak to the English speaking patients, mainly from the U.S., Canada and the U.K. These trials were international trials so we had a lot of non-English speaking patients who cannot do the VFQ questionnaire.

DR. SCHEIN: Is the retina community thinking it's standard of care to treat these patients with PDT, how do you get enrollment to a placebo group and physicians to participate? There is an inconsistency here.

DR. AZAB: It's been difficult.

DR. BRESSLER: First of all, some of us are not participating in it, so although I chaired many of these trials, I did not have equipoise in myself, nor did I think there was community equipoise to go ahead with that. That being said, I wish they didn't have to do the trial, but the industry made a decision that they want to have this available in some way through an FDA approval and if it takes doing another trial, they need to explain to each study participant coming in the results we just shared with you today, where I would think that most patients would not want to become a study participant. And then they have to recognize that they could get this treatment, and if they can't afford the treatment, maybe they would then want to enter the study.

I don't like that from an ethical standpoint because then we're doing trials only on people that can't necessarily afford the treatment, but that has evolved to what has happened because people have different roles that they're trying to fill. So I think people must be informed, and they're making an accurate decision, that they realize to the best knowledge of some peoples opinions, this is not something to do. But the

informed consent also says that the FDA has concluded there is no definitive evidence yet, because the FDA conclusion, I suspect, was just on the one-year three-line outcomes.

DR. DAVIS: I have Paul, Steve, and then Wade, and then we will move on.

DR. REDBERG: I have a follow-up on the quality of life issue.

DR. DAVIS: Well, why don't we come back to Rita, and then we'll try and cut it off, unless somebody squeezes my thigh or something.

(Laughter.)

DR. WALLACE: I have a question for Dr. Bressler. First of all, I appreciated your communication of how the evolving understanding of this is really quite dynamic, and it also was quite helpful to hear the discussion around lesion size, and also what seems like a beginning understanding of the importance of the trajectory of visual change. I also, though, wanted to follow up on what I think I heard you say about the ability to depend on the review of fluorescein angiograms over time to help us identify when there actually is the development of classical change versus other artifacts that may mimic classical change. It seems

to me that a great deal of sort of how we've gotten a toehold in understanding this has been to use the ability to differentiate between classical and occult, but what I believe I heard you say is that if we wanted to imagine a management strategy over time being able to differentiate serially, we need to discount our reliance on that test because of the occurrence of a variety of other things like scarring. So I just wanted to be sure that I heard that, and maybe allow you to comment on that.

DR. BRESSLER: Your summary is correct and I will just expand on it slightly, hopefully not to bring us to a higher level of confusion, to say that the entry criteria to try and make this applicable and generalizable to the world was something where we taught the ophthalmologists at a meeting what the entry criteria were. And then we said enter what you think meet these criteria. So this is what retina specialists who came to this training meeting will enter. And sometimes they entered things that they thought had classic but they weren't right all the time, but most of the time they were right, let's say 80 percent of the time they were not right or wrong, but they were in compliance with what a reading center independently graded to to provide uniform

interpretation. That's at baseline.
At follow-up, all the information that you heard about was their classic at follow-up. That is purely a reading center determination. We did not collect any information from the ophthalmologists at follow-up, did they think there was classic or occult, for the very reasons that we predicted, that it is hard to categorize it, there are other features as a lesion matures over time, that might look classic but you just don't see when it walks in. So this information about maybe some of the cases developed classic, that's a reading center determination. We don't know if ophthalmologists would have come up with the same conclusion, and there are many variables that come into that, that we believe it would be quite variable.
So we would say that they developed classic and I might almost put it in quotes, because it was an investigative item to help us further understand the disease, not to define how the physician should treat it.
DR. WALLACE: Do we have empirical data looking over time at inter-rater reliability, looking at those even in the center?
DR. BRESSLER: Only at the reading center.

DR. WALLACE: One would hypothesize, or you would expect higher inter-reader variability over time even of that group that was pretty consistent up front if what you're saying is true.

DR. BRESSLER: There is, but we don't have, I suspect, large enough numbers yet to detect obvious differences in the variability, comparing the variability at baseline to the variability at follow-up but there is, you know, in a qualitative sense.

DR. DAVIS: Steve.

DR. PHURROUGH: Just to follow on with that for a second, and then I have a policy question that somebody else may want to answer. So as I understand, the trial was referred patients who had a diagnosis of occult and no classic, the majority of them, ignoring the classic with good vision for a moment, and that diagnosis was not made by the reading center.

DR. BRESSLER: Correct.

DR. PHURROUGH: It was made by ophthalmologists in the trial or made by ophthalmologists who were referring to trial participants, or --

DR. BRESSLER: The former,

ophthalmologists in the trial who went through a training meeting and you know, a certification process. We gave them a quiz, did they understand it, if not a little tutorial to help them, until we were comfortable that they would agree with us most of the time, agree with a centralized center most of the time.
DR. PHURROUGH: So you're not uncomfortable that the control group which should have been comparing the treatment of verteporfin to a control group who did not have occult, in fact the occult control group had a large number of people with occult, I mean with classic, the follow-up readings from the reading center had a large number of those patients who supposedly had occult disease having classic disease when the trial started.
DR. BRESSLER: It wasn't a large number, I suspect. There were people that entered the trial with classic, but they were purposely entered.
DR. PHURROUGH: For those who were in the control group who supposedly had only occult disease when they were referred, they had a reading early, early in the course of the trial by your reading center, that had classic disease.
DR. BRESSLER: Might have, but that was a

very small number.
DR. PHURROUGH: I thought it was about a third.
DR. BRESSLER: We're getting a little, I think mixed up. It's true that the VIP trial had cases of both occult with no classic and some that had classic with good vision, but those were purposely enrolled by the ophthalmologists.
DR. PHURROUGH: My understanding was for those who just had occult, one-third of them had classic after the -- when they were referred they had occult but shortly after that by some reading they had classic. Is that incorrect?
DR. BRESSLER: No, I don't think so.
DR. AZAB: All the information we had in the follow-up had been read centrally. The old what we reported as occult with no classic is a definition of a center reading center. You are referring to the follow-up when they followed up, and the follow-up read by the reading center was started at 12 months, so the earliest they could have recorded classic was the 12 months. Having said that, there are grading the angiographic criteria that showed some classic component at the 12 and the 24 months, not at the referral. At the referral, they entered the trial by

a diagnosis from the treating center but all the angiograms were read centrally at baseline.

DR. PHURROUGH: And centrally was the basis for entry into the trial?

DR. BRESSLER: No. The inclusion criteria were the basis for the trial, so each individual investigator confirmed in their mind that the patient met the criteria to become a participant and then they enrolled them.

DR. PHURROUGH: And then there was very good comparison for those who supposedly had 100 percent occult between the referring ophthalmologist and the reading center at entry to the trial.

DR. BRESSLER: Not perfect, but pretty good.

DR. PHURROUGH: Let me ask my policy question, and this is more of an open question and you may want to answer. CMS in general almost exclusively for items and services that need FDA approval, provide coverage for things that have FDA approval. There are occasions where we look at doing approvals for off-label indications but in general we leave that up to the local carriers to make that call, but sometimes we look at things on a national basis that are off-labeled. But in general, that's

only things that are off-labeled because they have never been presented to FDA. Here we have a particular service that has one FDA approval and had a presentation to FDA to get the approval for the indication we're discussing and the FDA rejected it or at least required more information. So it seems to me we are now embarking on a potentially precedential event at CMS where we will say we are going to reimburse for something on a national basis that the FDA has said there isn't enough evidence for us to make the call at the FDA, versus the other off-label approvals where we have said we will do an off-label approval where the FDA has never made a call. Why should we make that precedential step?

DR. AZAB: I just want to clarify a point, it may be the same thing, but I want to clarify that we have not submitted a file to the FDA for this indication and it got rejected. That was a meeting with the FDA where they suggested that we will have a better chance in the approval by getting the second trial because they said that for this indication, we will require two trials, and that's why we are doing the second confirmatory trial, but we have not actually submitted a file for the FDA.

The other also clarification, Dr. Phurrough, is that there is a national noncoverage for this indication, which means that the local carriers, if they want to cover it, they cannot cover it currently because of the current national noncoverage.

DR. BRESSLER: I would only close by saying I definitely am not a policy person. I do have an interest in public health policy and society issues, and I think that's exactly why you have panels for something like this, because in general, it probably doesn't make sense, but I think this is an example where it does based on the evidence that we shared with you, and I think it should be done very carefully, but I'm very comfortable with the information that we have, and we have an unusual situation here where I think in this case, the exception should be made.

DR. DAVIS: Wade.

DR. AUBRY: My question had to do with the FDA and the ethics of randomization in the other study, but I'd like to ask another question, and that is of Dr. Williams of the AAO, and that has to do with the -- I was interested in the survey that you presented, both 2001 and 2003, regarding the use of

watchful waiting as opposed to OPT in patients with occult lesions, and really only a minimal decrease. And these are basically the opinions of practicing ophthalmologists; is that correct?

DR. WILLIAMS: That's correct.

DR. AUBRY: And I wondered if you had any more information. Are these patients who had fairly good vision, or is there any other information on the patient characteristics that would lead such a large number of practicing ophthalmologists basically doing something otherwise than what has been listed here as a standard of care?

DR. WILLIAMS: This is the first time in my life I have ever been confused with Dr. Packo.

DR. AUBRY: Excuse me, the ASRS, excuse me.

DR. WILLIAMS: I will ask Dr. Packo to answer that question.

DR. PACKO: One of the things that given the time constraint I didn't point out is that this survey is fraught with all sorts of potential problems, because the survey was sent out and asked a hypothetical situation, what would you do. There was no attempt to look at the true behavior. We took it as a trend or suggestion of what would happen. They

were given a hypothetical with more information of you know, a fictitious vision at that point in time. We did not give an indication that there was blood present or that there was a suggestion that this was an active lesion that, for example as Neil has stressed in the trial, these were occult lesions that were most likely going to progress and do something. So again, that was a shortcoming of that survey, and I think that was one of the reasons too why the observation group was so high.

It still struck me that it was still a strong choice by almost the same amount that chose observation in the year following. It was more people that chose photodynamic therapy despite the continued frustration there.

Related to this too, I think our look on that in the sense that people were choosing photodynamic therapy in the community and the reason I said this really is important in defining standard of care and what a reasonable and competent physician would do, and I think Dr. Bergthold, you commented that you would want more than a reasonably competent physician. I think from my position, I would want the best physician that I could find but the reality is we have all sorts and types of physicians and we

need to define the legal definition of standard of care just as that, this is what a reasonably qualified person would do. And this survey was attempting to gather some information to answer that question, what are reasonably qualified people doing with this data.
And as Paul said, the survey just gave us a general trend of whether people were still generally using this, despite the fact that the CMS has mandated a noncoverage.
DR. DAVIS: I think we will wrap us this item on the agenda with Rita.
DR. REDBERG: I just wanted to come back to the quality of life. I appreciate everything that you have already explained, but the reason I think it is so important, just like every one of the patients in the room said, what's really important to all of us is that we maintain our vision, are able to see and get along and drive, and I'm trying to understand how closely changes in visual acuity correlate to visual function, and that's why I was coming back to that visual function questionnaire, because it seems to me that's the closest we have to kind of get to visual functioning and what we can see.
So if I understood correctly what you

explained before, if I was going to see you as a patient and I had classic or occult lesions in one eye but the other eye still had better visual acuity, I would not see any benefit from treating that particular eye, and what you might suggest to me is wait until -- it's likely this other eye will be involved at some point, wait until that eye is involved, because if you started just doing the therapy on my eye that was involved, even if I had an improvement in visual acuity, it wouldn't make a difference in my functional status because I'm really using my better eye, which isn't involved for treatment. So you would wait until both eyes were involved and then treat the worst eye; is that correct?

DR. BRESSLER: I wouldn't wait until both eyes are involved, only because this is very often a bilateral condition within five years and you can't go back in time then and treat it. You can only treat it when they first present, or let's say sometimes within three months, sometimes you can wait maybe even up to six months, but not necessarily even six weeks for some people. So we have to make a decision, do we want to treat this eye now to try and get the maximum function for it, because at the time

that your other eye becomes involved, which will happen in one out of two of you, that second eye may end up being the worst eye and all of your function, where you end up on that average physical function, may be dependent on what where we got that first eye to. Because with both eyes involved, the visual function is most dependent on that first eye. Now, there is a little bit where the second eye comes into it, and you're not going to that, I think with 100 or 200 people. We may find it in some of our other trials that have 800 or 900 people, so there is a little bit that we suspect that the second eye helps as well, not that is why we would not wait on the person who comes in with their first eye involved. We don't know how badly that second eye is going to become. It has a high risk of becoming involved.

DR. REDBERG: So you would say to me, I wouldn't expect any improvement in my visual functioning but that in a number of years with that 50 percent chance that the other eye would get involved, then we would be glad we did it.

DR. BRESSLER: Correct.

DR. REDBERG: And then take that 5 percent risk that I could have severe vision loss.

DR. BRESSLER: Correct, that's the simplest. And remember, that 5 percent risk, while it's important, in three months, the same number of people who were randomly assigned to observation, 5 percent of them already developed severe vision loss, so there's the immediate and then there is the left alone, but that's correct.

DR. DAVIS: We're schedule to finish at 3:30 and we're going to do that. I realize a lot of people have planes to catch. So we'll obviously have to make adjustments in the rest of the agenda and we will see how that goes, but we will try and reserve the bulk of the time to answering these several voting questions and discussion questions, but before we do that, I do want to turn to Barbara and Wade to see what comments, if any, they would like to make with response to these two items on the agenda, lead methodological reviewer presentation and lead clinical reviewer presentation. Barbara.

DR. McNEIL: Well, I actually don't want to say anything. All I can say is that before I decided to say nothing, I redid my slides three times as a result of the presentations that were made this morning. And I think that most of the issues that I had been interested in talking about related to

analyses of the whole cohort and the subcohorts, as well as the various issues relating to confounding, what was really influencing what. There were a number of other issues that I think got brought up in the CMS presentation and at various points during the day, but I'm not quite sure they're as salient as they need to be relative to the two that I just mentioned. So I'm happy to pass on the rest of my prepared remarks.

DR. DAVIS: All right. Wade.

DR. AUBRY: Also, my presentation in view of all the clinical input we have had today is probably at best passed over in place of some committee discussion about what to do with this issue today.

I do think that the VIP trial and what can be gleaned from that is the key issue and whether the methodologic points that are brought up are significant enough to question whether that evidence is sufficient or whether a second try is necessary to answer the questions. And I do recognize the comments of the experts and the investigators and sponsors and specialty societies, but I think that ultimately the question that we're being asked is one of evidence and whether there is sufficient evidence

for making a decision today, and whether we have all the evidence we need.
DR. DAVIS: Thank you. Let's move forward to open panel deliberations and consideration of these voting questions and discussion questions. Before we jump into the first one, I do want to clarify a comment that I made at the beginning of the day in regards to my conflict of interest disclosure. I mentioned that I'm on the board of trustees of the American Medical Association. I wanted to clarify for the record that I'm not here today representing the AMA and the AMA does not, as far as I understand, have any policy on the matter that we are considering.
Moving on to the voting questions, and we'll take them one by one and present the wording to you, and you see it here on the screen and everybody has a copy of it in writing, everybody on the panel. And maybe I will just read it so that we are all reminded of exact wording, and then we can have discussion and get to a point where we might consider what action to take on it.
Is there adequate evidence to draw conclusions about the net health benefits, that is, whether or not the risks and benefits of treatment

outweigh the risks and benefits of nontreatment of ocular photodynamic therapy with verteporfin in routine clinical use in the population of Medicare beneficiaries who have age-related macular degeneration and occult with no classic choroidal neovascularization.

So let me just open it up now to discussion among the committee members of this particular question. Alan, and then Barbara.

DR. GARBER: Well Ron, I find myself for the first time ever saying I have trouble answering the question about whether the evidence is adequate, and let me explain why I feel that way. We heard two, I think some excellent presentations from both CMS and the requestor. And there are a lot of facts that first came out at today's presentation that were not in the readings that we received. And I think, it's not very easy to reconcile, and I'll give you one example that I find particularly hard to square, and that is how much of these hypotheses were post hoc in some sense and how much faith can we have in the outcomes?

My sense is that we could answer this question with more time to absorb what all the hypotheses were that were really tested. There is

the subgroup analyses and it sounds as though they were probably done without knowledge of the data from this trial. It seems to me legitimate from my point of view to draw on results of the TAP trial to change what hypotheses you would address in the VIP trial, but I found that it was very difficult to really absorb everything that was presented today and to try and reconcile some fairly conflicting statements. Let me add, by the way, that I think all of us here, I certainly speak for myself, but I suspect the entire panel shares this view, believes that anything that would significantly reduce the development of visual loss from macular degeneration is worth pursuing and worth covering. That's really not the issue we're grappling with. It's is it established that for this indication that this treatment actually works, and I suspect that we can answer whether the evidence is adequate by looking at all the evidence a little more closely. One other brief thing about the trial. Normally I would say if there is a trial that's going forward that addresses the exact question, we shouldn't make a decision until the results of the trial. But I'm also aware of the kind of message that we would be sending to manufacturers if we said

basically you'd have a good shot at getting coverage if you hadn't done the trial, but now we're going to delay it for a couple of years because we want to see what the trial does. And I think that's absolutely the wrong kind of message because we all benefit by knowing better which treatments work.

So this is kind of a question to Steve, whether it's even possible to conclude today, and this is a little bit off this question, but whether it's even possible to make a recommendation that would lead to coverage until the results of the trial are available and then a relook at this whole issue after we have the results of the trial.

DR. PHURROUGH: Just in response to that, again, we're not asking you to make a recommendation for coverage. We're asking you to tell us whether you as a group think there is adequate evidence and that adequacy includes both volume and quality, and then we will take whatever recommendations you make on that adequacy of the evidence and make a conclusion as to how we should change or not change policy.

There are a whole host of options in changing policy. We could remove the national noncoverage and make it nationally covered. We could

maintain noncoverage. We're trying to get away from it, but I guess we could say we will remove noncoverages and leave it to carrier discretion. I don't particularly like that option but that is something we could do. We could say it's covered in the context of a trial. So there are a lot of policy options that we have, but the issue we want you to address is whether you think the evidence is sufficient or not, and we really encourage you to go forward with that this afternoon, recognizing that you have some concerns about whether you have had time to digest the information or not.

DR. DAVIS: Barbara.

DR. McNEIL: I thought I was conflicted about this but I'm not conflicted about the following statement and that is, I have both a personal and professional interest in worrying about people with chronic eye diseases, so I really want to make sure we get this one right. And I want to make sure that if we have a good treatment we get it to the right patients and if we don't, we don't.

So my concern is, we were all faced with multiples piece of new data today, and I found it very difficult to frankly absorb them and to sort out some of the we/they and some of the very new pieces

of data that we got from some of the requestors. Some of these related to the confounders that I talked about earlier, some of them related to the area of function that Rita raised and whether that's a reliable or a valid end point for studies like this. And I think that after Dr. Bressler's discussion, it seemed to me maybe it wasn't something that was an important end point, but rather we should go with the 15 and 30 lines.

So I'm inclined to say that if it were possible -- and the other comment is, I really am not wild about waiting for the results of a new study, because I think that puts us too far down the line and I think that sends all kinds of messages. I would much prefer us to make a decision and if something happens with the new study that's negative, we revise our thinking at that period of time, but I personally would like to have more time to think this over, so if at all possible to get copies of the data that were presented and to have some kind of resolution of the subgroup analyses, or the ex ante ex post hypotheses that were proposed, I would feel a lot better, and I personally would like to ask Steve and the rest of the group if I could make a motion that we get such information relatively rapidly, like

within the next couple of days or certainly within the next week, and that we reconvene within a very short period of time to make a motion. If we have to make a motion that answers this question, then I think I'd be prepared to do it on the basis of more data.
I frankly would rather answer a question that had to do with a different definition of the populations defined according to size, but that may not be possible, I don't know if that's possible. But in any case, I feel very uncomfortable answering question either way today on the basis of this rapid infusion of data, some of which apparently just got published, and I'm just not quick enough to pick it all up. So, I would vote to delay the vote.
DR. DAVIS: Barbara, maybe for the sake of discussion, if you want to make a motion, and then if there is a second then we can discuss it and decide what to do with that motion at that point. But if you want to hold off, we can also take other commentary. It's up to you.
DR. McNEIL: I will make a motion if I can make a motion.
DR. DAVIS: Go ahead.
DR. McNEIL: The motion would be that the

voting panel get more information from the requestors about the new data that was just presented today to us, relatively rapidly, and that we be given an opportunity to reconvene relatively rapidly to make a judgment on the voting questions one and two.
DR. DAVIS: And let me just ask you, would that include the idea that CMS would also present to us their views in response to any additional information that was provided to us?
DR. McNEIL: Well personally, yes. I would like to have a resolution. There was clearly a we/they kind of discussion going on and I would like to have resolution of that off-line so that we could have a deeper discussion about the real facts.
DR. DAVIS: All right. We can tweak the wording. Let me understand that people around the table understand the gist of it, and let me just see if there is a second and if there is, we can go on to discuss it.
DR. GOODMAN: I will second.
DR. DAVIS: Oliver, you were the first to have your hand up. Did you want to discuss this motion, or we can put you in the queue for after we dispense with the motion.
DR. SCHEIN: I think they are related,

because the wording of this question reflects the FDA history and the first approval, and may no longer make sense. And I think like Barbara, I would like to see considered that the question be phrased differently, and that may require this review of new data. I think this is an anachronism now to phrase the question this way.

DR. PHURROUGH: In this particular instance, CMS can go back and address the issue of the question, but the panel does not have the option of modifying either of these questions.

DR. DAVIS: Yes, Anne.

DR. CURTIS: Regarding this motion, I just want to state a very strong objection to that approach. I have, you know, listened with everybody else today and read the materials before we got here. I understand the concerns of CMS in looking at the data that they've looked at. I've heard the answers, particularly from Dr. Bressler and everybody else who has explained their views today. I've been satisfied with the answers. I think we have enough evidence. I don't think that tweaking this or looking at some extra information is going to make this decision any easier. I think the evidence is there.

I would be reluctant to, or I guess a

better way to say it is I object to delaying a decision from today, because coming back is not something we can do quickly. I mean, you're talking about convening another public panel which, Steve, you can correct me if I'm wrong, but it would probably take another couple of months to get that to come about and you know, there are patients who are looking for this therapy today. And so, I think I can adequately answer these voting questions today and that's what I would like to see happen.

DR. PHURROUGH: CMS's preference is that you go ahead and make a call on what you have today, recognizing its limitations. We would prefer you go ahead but that is your option, if you say I can't do it without further, we can't tell you not to do that.

DR. DAVIS: I think just to help us make the correct decision, I think the question that everybody is going to have to ask is maybe there might be adequate evidence out there but I just don't feel I have it today and therefore, if I feel that way I might be inclined to vote no today, whereas if you gave me another couple months and provided that information to me, then I might be able to vote yes in a couple of months.

But, I don't mean to put any thoughts into

peoples minds but I think that's the issue that we each have to decide on. Steve, I think you were next, and then Greg.
DR. GOODMAN: This is a question I actually wanted to ask Dr. Stone earlier. I'm just wondering if there is any way to get clarification on the he said/he said debate here. I mean, Dr. Azab very clearly said what were called revised statistical analyses were in fact complete statistical plans which were not intended to be outlined in the protocol, and Dr. Stone interpreted differently. And I'm just wondering if he could spend a minute, I don't want to use up our precious time here, but if Dr. Stone got up and said you're exactly right, I misinterpreted, that would be important information for me, but if he was going to hold to what he said before, that would be something that couldn't be resolved right here.
DR. DAVIS: Dr. Stone.
DR. STONE: I have the original protocol and all the amendments for both trials right here, and in both trials in the initial protocol is a statistical analysis plan.
DR. GOODMAN: A less detailed on, though.
DR. STONE: No. As a matter of fact, in

each trial there is a second and in the case of VIP, a third statistical analysis plan. They all carry the header for the trial as formal amendments to the trial as inherent parts of the trial, and we asked to have all protocols and amendments to the trial. For example in the TAP trial, it is Amendment Number 8.

DR. GOODMAN: You can probably cut to the chase. You are basically holding to the way you presented it before.

DR. STONE: The formatting is the same, the wording is the same. In one case they did add some shells for statistical tables, but the entire discussion and analysis is exactly the same format and is of the same content, and I explained what the differences were in contrast.

DR. GOODMAN: Thank you.

DR. DAVIS: If the committee doesn't object, I will give Dr. Azab, who is raising his hand, an opportunity to make a quick response.

DR. AZAB: This is, I also have the protocol and the original analysis plan here, and they are available with Post-Its with all the sections that includes all the analysis being prespecified in the original analysis plan which is

dated October 1999. ICH guidelines clearly states the protocol has a statistical section which has all the principal features, and the analysis plan has the table shells and all the analysis we do, that's just standard of practice of doing clinical trials, and that's FDA approved.
Dr. Stone referred to the TAP trial. This is approved everywhere, including FDA, so how come we didn't follow the methods that are not standard? The VIP is approved in the European Union, who wrote the ICH guidelines. I'm not sure that this is really something that was appropriate that we spend discussion. I mean, the evidence are there. Even if there was revision of the analysis plan, the primary end point as we showed you here, and we actually made a mistake, and would we revise an analysis plan and choose a primary end point that would not work? It would have been a very bad job of revision.
And the secondary efficacy variables that I showed here are all detailed in the protocol. Whether the revisions were made or not, revisions of analysis plans occur all the time in very long-term chronic disease studies, but none of them affected the efficacy variables that we saw today.
DR. DAVIS: Thank you. Further discussion

about the motion? Oliver.
DR. SCHEIN: I was going to say this is a nonissue, this statistical argument about the process. There is a consistency to the data across time that speaks for itself, and the question really is what you do with a treatment which has a very very limited effect.
DR. DAVIS: Greg and then Bob.
DR. RAAB: I was only going to argue that the CMS provided a litany of problems they perceive with the trial and they were responded to in a short fashion because that's all the time they had once it was posted. We all heard it, and I think it's an impressionistic thing, and I think we ought to vote.
DR. DAVIS: Any other comments on this motion? Bob.
DR. BROOK: Before we vote on the motion, the FDA thing is concerning to me and I didn't get any information. I don't know whether we have people in the room who can answer this question about what the FDA really did here when this informal discussion was had to approve this for the nonclassical, the occult lesion. I don't really understand what happened. There is nobody from the FDA here, I trust, or is there, or can we at least be informed

about what happened or is that off the record?
DR. PHURROUGH: The FDA will not discuss with us or anyone else presentations to them that are not formal decisions, so we are unable to get FDA input and require them to tell us what they think happened.
DR. AZAB: I can give an account. I mean, that was a formal meeting and formal minutes are there at the FDA and in our records. We had a formal meeting in April 2001 with the division. We discussed the data from the VIP and they said because the time initially -- just to give you a history, Dr. Brook, the initial discussion was for a supplementary indication and not really a very different disease. If you have one trial supplementing the two TAP trials, and the TAP trials by the way were two independent trials powered independently, their manuscript was combined but the two trials were powered independently, so the analysis was independent.
They said one trial would supplement the two TAP trials if the results are very similar. And when they saw that the VIP trial, the results were not similar in that the primary outcome of the three-line loss, which was the same as TAP, was not

evident in the VIP, it only happened at two years, they said the results are really not similar, the one trial would not be adequate, this could be a disease behaving differently from the predominant classic, we would need confirmation and so for this one we have to follow the guidelines of two adequate and well controlled studies, and that's what we've done. I believe the meeting was in April 2001.

DR. DAVIS: Okay. I don't see anybody else waiting to address this motion. Let me just articulate what I think it is, and Barbara, you correct me if I'm wrong. But I think the motion would be to request that more information be provided to the committee from the requestor and/or CMS to answer any questions or gaps in knowledge that the committee may have.

And I assume that if we voted this through that we would give people an opportunity over a couple of days to present questions that we would like them to answer, or materials that we would like to be able to inspect, and then we would meet as soon as CMS could arrange for us to meet again and reconsider question one. Is that what you're desiring with this motion?

DR. McNEIL: It is.

DR. DAVIS: Does everybody understand that? Okay. Before we vote on that motion, Michelle is going to read us some instructions about who can vote.

MS. ATKINSON: For the record, the voting members present for today's meeting are Barbara McNeil, Wade Aubry, Robert Brook, Anne Curtis, Susan Bartlett Foote, Steve Goodman, Karl Matuszewski, Margaret Piper, Rita Redberg, and Paul Wallace. Dr. Davis will vote in the event of a tie. A quorum is present and no one has been recused because of conflicts of interest.

DR. DAVIS: Thank you. And we have some instructions on the agenda on how we are to proceed with voting, and that is that each person is asked to give the reason for their vote and then to indicate what their vote is. So I assume that when you give the reason for your vote, it can just be a sentence or so, it does not need to be a five-minute speech. So, I guess we can go around starting with Barbara.

DR. McNEIL: Well, I vote for the motion since I made it, and I made it because I thought there were lots of pieces of new data that I would feel much more comfortable in digesting fully so that I can make an informed judgment about question number

one.
DR. DAVIS: Bob.
DR. BROOK: I vote against the motion. I think to answer question one, we have all the data we need and we can't reformulate the question to a better question, so we have plenty of data to answer this question right now.
DR. DAVIS: Why don't we just proceed, and people can speak up without waiting for my recognition.
MS. BARTLETT FOOTE: I vote no. I agree that we have enough information to make a decision based on this question at this time.
DR. MATUSZEWSKI: I vote no. I also concur, we have enough information at this time.
DR. CURTIS: I vote no. I already stated my reasons before.
DR. WALLACE: I would vote no. I believe we have enough information.
DR. PIPER: I would vote no.
DR. GOODMAN: Even though I seconded it, I will vote no. I got some clarification and I think it's a very difficult decision, which is still going to be difficult in two months.
DR. REDBERG: I vote no. I think there

are some unresolved questions but we have enough data to vote on this question.
DR. AUBRY: I vote yes, even though I share some of the sentiments of the people who voted no. I do feel there is a significant disconnect between the presenters and requestors for the change in Medicare policy and CMS response, and I do feel that there is some data that was presented here that would be better digested and turned around quickly for a decision. And I share Barbara's opinion that it's in the best interest of the Medicare program for that decision to be right.
DR. DAVIS: So the motion obviously fails with two votes for and eight against.
So let's proceed to answering this particular voting question, and I will open it up for any further suggestion, if there is any. Yes, Susan.
MS. BARTLETT FOOTE: I just have a point of clarification, and this is my first time so I hope I am not saying something that's obvious. It's clear to me from the discussion that the weight of the evidence varies under certain circumstances, and so when we vote on adequate evidence and it's defined as occult with no classic, and there is no discussion about different, you know, the size of the lesion or

the evidence of progressive loss or any of those other issues that we talked about, when we vote on this, are we saying it's adequate for the entire group that's in the last line, or are we going to be permitted to make some distinctions?
DR. DAVIS: My take on that is that we have to answer this question as it appears before us, but if you look at discussion question two, that might be an opportunity to point out where additional research might help to clarify what subpopulations might benefit more than others.
DR. PHURROUGH: The vote is specifically on this question, though we may in fact as the Agency take your recommendations along with the other things that we have heard today, and our decision could in fact be something that is somewhat modified from this, but you must vote on this particular question.
DR. DAVIS: Greg.
DR. RAAB: I was going to chime in and say that in the course of the three years or so of this committee, Sean Tunis and you yourself, Steve, have sat here and reassured the committee it would lean on the context of the debate and the consideration of the issue in drafting an eventual coverage decision. So if we focus on evidence, the issue of FDA and the

nomenclature for this could be a coverage issue.
DR. DAVIS: Steve, and then Bob.
DR. GOODMAN: This relates I guess to the phrasing, which I know we can't change. But draw conclusions doesn't say anything about the strength of belief in those conclusions. I can draw a conclusion and think that the conclusion is correct with about 75 percent probability. So anything is enough to draw a conclusion. If the statement were a conclusion beyond a reasonable doubt or whatever degree of certainty we want to have for major policy recommendations, if that's the threshold, I would vote differently than a conclusion with a lesser degree of certainty. And I think one of the troubling parts here is we're in this middle ground where it's not beyond a reasonable doubt but it's clearly, at least I would say personally well beyond 50/50. So we're in that middle ground that's very very difficult and typically these conclusions come with some grays. Now, if the graying is going to come in the second half and it can be qualified there, then I'm more comfortable, but a conclusion that's only 51 percent certainly is in some sense not a conclusion. I think that's one of the reasons why it's such a difficult question to answer.

DR. DAVIS: Bob.
DR. BROOK: I'm confused, to be honest, about how coverage is being used here. A lot of the comments that I heard people make relate to the appropriateness of the professional decision. From the work we've done, we know that that is terrible in a large percentage of the procedures that Medicare covers, and that's a fact of, you know, of the field. But you don't uncover the procedure, you try to fix the problem. And what I'm viewing is, are we separating the concept of coverage from responsible behavior.
DR. DAVIS: Bob, I hate to interrupt but I do think we need to stick with the wording in front of us.
DR. BROOK: Well, I'm not changing the question. This is a coverage question.
DR. PHURROUGH: This question is do you believe the evidence is strong enough to reach any conclusion, whether the conclusion is it doesn't work or it does work, is what you have been presented today enough to draw a conclusion.
DR. CURTIS: If I could --
DR. DAVIS: I had Wade on my list and then Anne, if you don't mind holding off.

DR. AUBRY: It seems to me that this question refers to two things, one, is there adequate evidence to reach a conclusion, and secondly, is that conclusion that there's an improvement in net health outcomes that the benefits outweigh the harms. That's what the parentheses says. So unless I'm reading this wrong --

DR. DAVIS: Whether or not, the words or not allow it to go a different way as I read it. But when we get to voting question two, I think we get into the direction of the effect or the benefit.

DR. AUBRY: I stand corrected.

DR. DAVIS: Anne.

DR. CURTIS: I would like to suggest that the fact that we voted down Barbara's motion means that if you took a vote right now we would vote yes on this, because if we didn't have the evidence, we would have had to agree with Barbara. I mean, if we could vote on this, really the crux of the matter is question number two, you know, are we going to say yes or no, we agree with it, but here it's just whether there's adequate evidence.

DR. REDBERG: I don't think that's what Barbara's motion was about. Her motion was do we have it now or would we have it two months from now,

and I don't think we will have it in two months, anything more than we have now.

DR. DAVIS: I think we're going to finish with the discussion momentarily. I mean theoretically, someone could just vote no. Barbara wanted to postpone voting. We could vote yes, we could vote no at this point, I believe. Any further discussion before we proceed to voting on this question? If not, let us proceed.

DR. BERGTHOLD: Call the question.

DR. DAVIS: Is there a second? I don't know that we need that to vote on this.

DR. CURTIS: Second.

DR. DAVIS: But hearing no objection, we will proceed with the vote, how about that. And why don't we start this time, if it doesn't cause too much confusion, from the other end of the table. Wade, do you want to begin?

DR. AUBRY: I vote yes, although I would prefer to have this delayed, as I mentioned. I do think that there is sufficient evidence to answer this question affirmatively.

DR. REDBERG: I vote no. I would like more evidence, but not that I see coming in two months.

DR. GOODMAN: I vote yes.
MS. BERGTHOLD: I don't get to vote but I do get to say something, right?
DR. DAVIS: Proceed.
MS. BERGTHOLD: Actually, I don't like the way the question is phrased and I think when it is discussed and finally voted, we'll have to deal with it, but that "and" is very disturbing, that "and occult" because it sounds like you're voting that you can draw conclusions about its use in the routine clinical use in the whole population of medicare, as well as with those with occult, so in your coverage decision, I think that needs to be clarified, because to me that's confusing.
DR. DAVIS: I think the "and" combines age-related macular degeneration with the occult with no classic choroidal neovascularization, just from a grammatical point of view, unless somebody corrects me. Proceed.
DR. RAAB: I would like to comment that there is enough evidence and there is not enough evidence to support a national noncoverage decision, which is what we have right now.
DR. PIPER: I vote yes, there is enough evidence.

DR. WALLACE: I vote yes, with the same discomforts that I think Steve captured well earlier.
DR. CURTIS: I vote yes, I think we have you have enough evidence.
DR. MATUSZEWSKI: I vote yes. I don't think VIP was a perfect trial, few are. I think it was a modest trial and it showed some modest results.
MS. BARTLETT FOOTE: I vote yes. I agree that we could use more evidence, we could use stronger evidence, but I think we have enough to go forward and I would hope we would be able to express those doubts about scope in addressing the second question.
DR. BROOK: I'm going to vote yes, but I do it with the trepidation that it's not the lack of efficacy evidence that we have a problem with, it's going to be the lack of the way it's implemented in a major way to get the benefit versus the risk.
DR. McNEIL: Is it possible to abstain?
MS. ATKINSON: Yes.
DR. McNEIL: I abstain.
DR. DAVIS: And it's apparent that question number one is approved in the affirmative, and Michelle will give us the vote for those of us who weren't keeping track.

MS. ATKINSON: It was eight for, one against, and one abstention.
DR. DAVIS: Thank you. So we will proceed to voting question number two, which is now projected on the screen, and we'll have some brief discussion and then a vote on this one.
If the panel answers the first question affirmatively, does the evidence demonstrate that OTP with verteporfin treatment improves net health outcomes in treating age-related macular degeneration in occult with no classic neovascularization and if so, what is the size of the benefit in patients receiving the treatment?
Now if we followed parliamentary procedure, one good way to handle this would be, since this is a combination question, we would handle the first part of it separately, unless the committee objects. So if there is no objection, why don't we answer this question through CNV, closed parentheses?
Let me open it up to discussion.
Margaret.
DR. PIPER: I would rather tie my answer together than answer separately, but that's just a preference.
DR. DAVIS: Let me suggest that we

continue with my suggestion. If someone wants to make a motion to keep it as one total question, we can do that, but I would prefer to keep it as two separate discussions.

DR. BROOK: Isn't that the question one we just voted on.

(Inaudible colloquy.)

DR. BROOK: This says improve net health outcomes.

DR. BROOK: That's what question one said, whether or not the risk and benefits --

DR. DAVIS: Whether or not. You could have concluded that there was no benefit, the key words being "or not".

DR. BROOK: I got it.

DR. DAVIS: If we could go back in time, we could rework these questions and prevent some repetition or lack of efficiency, but why don't we proceed with the question that we have and take this through CNV. Any discussion? Yes, Oliver.

DR. SCHEIN: As a nonvoter, maybe this is an opportunity for those who agree to say yes and in certain situations, and then bring in the lesion size and qualify the --

DR. BROOK: This can't be changed either?

DR. DAVIS: No. You can vote on the wording as is and then if you want to make a separate commentary or propose a separate motion for a separate conclusion, I presume that would be in order, but first we have to deal with this as is.

DR. PHURROUGH: But you have to do all of this in the next 19 minutes.

DR. DAVIS: Steve.

DR. GOODMAN: Well, discussing substance of the question, it was acknowledged that net health outcomes actually were not measured in this trial. We have visual acuity measures and other such things, so it's a bit of leap, and you would have to be fairly certain that the size of the visual acuity benefits were fairly large to then be equally or moderately certain that this translated into net health benefits.

DR. REDBERG: I would say they did do visual function questionnaire but didn't feel that it was adequately done and that is why I thought there was not adequate evidence. So I think net health outcomes were measured but there were some limitations to that measurement and I was disappointed to here that the next trial did not include a visual function questionnaire, and I

understand the limitations.
DR. DAVIS: Further discussion?
DR. MATUSZEWSKI: Health outcome, I mean, could be defined as preservation of vision. You're not just going for quality of life and functional outcome, so I think there was a health outcome that was reported.
DR. REDBERG: I don't really care what my visual acuity is, but I care whether I can see and get around, and I mean, would you care what your Snellen score is as long as you can see your children and drive and do all those things, that's what you're talking about, not your score.
DR. DAVIS: I don't know that we have time to debate what health outcome means and whether it includes a quality of life component. Any further discussion? Let's vote on this. I might have tried to start the voting in the middle this time but that could cause all sorts of confusion, so Barbara, back to you.
DR. McNEIL: I think I still have to abstain.
DR. DAVIS: Bob.
DR. BROOK: Yes, I think the evidence supports that if it's used according to some of the

conversations that we have heard about today, I would urge CMS to make sure it's used in that manner.
MS. BARTLETT FOOTE: I would say yes, but I hope in the next three lines we address, we can deal with the issue of scope.
DR. MATUSZEWSKI: Yes on the net health outcome.
DR. CURTIS: I vote yes. I think we've got enough evidence from what we heard today to say that there is not a huge benefit but a modest and a positive benefit for that therapy.
DR. WALLACE: I would vote yes, but with discomfort, some discomfort around the definition of the word net, I think we're putting a lot of things in there, but it crosses my threshold for saying it is more good.
DR. PIPER: Yes, with a similar discomfort and with concern that limitations can be adequately and accurately drawn and applied.
DR. GOODMAN: I would say I guess I have to come down on yes, reasonably certain that it exceeds zero, but this question of if so, what is the benefit, I think that's where the crux of the matter is, and whether we're reasonably certain that that exceeds some minimally important threshold I think is

very certain.
DR. DAVIS: Hold on that until the next vote on the size of the benefit.
DR. GOODMAN: Okay.
DR. DAVIS: So your vote again was yes?
DR. GOODMAN: I will vote yes on the improvement.
DR. REDBERG: No.
DR. AUBRY: Yes.
DR. DAVIS: That motion carries and the vote was eight in favor, one against and one abstention. So now we will address the size of the benefit in patients receiving the treatment. Any comments?
DR. AUBRY: Don't you have a slide that lists the categories for evaluating.
DR. DAVIS: Guidelines for evaluating effectiveness, which is in your packet. So we have eight categories of effectiveness and we're to pick one of these? Is that what you're saying, Steve?
DR. PHURROUGH: Yes.
DR. DAVIS: For those of you who haven't found it yet, the highest category is breakthrough technology, followed by substantially more effective, followed by more effective, followed by as effective

but with advantages, and then as effective and with no advantages, and then less effective, and so on, but I don't think the rest are pertinent here.
DR. REDBERG: This assumes we're comparing it to another treatment.
DR. PHURROUGH: The comparison here is to no treatment in this case.
DR. DAVIS: I thought like with the second one, substantially more effective than, I thought it was existing standard of care.
DR. REDBERG: Compared with established services or medical items, it says here.
DR. DAVIS: Okay. Anne.
DR. CURTIS: There is no alternative treatment for this so I think at a minimum we would have to say more effective; it's more effective than doing nothing. I don't think anyone here is going to go breakthrough technology or anything like that. I think there is a real positive benefit and I think it is certainly better than watchful waiting with these patients, so that's where I put my first nickel in.
DR. DAVIS: Would you like to make that a motion?
DR. CURTIS: Okay. I'll make a motion that we categorize this therapy as more effective.

DR. DAVIS: Is there a second?
DR. AUBRY: Second.
DR. DAVIS: Further discussion?
DR. AUBRY: I think it's the only one that makes sense in this entire list.
DR. BROOK: I would argue that it's substantially more effective, given what we have labeled to be substantially more effective in other areas of medicine. If you believe the evidence and you can prevent three or four people out of a hundred from becoming blind, you know, compared to what we do for pneumonia, heart attacks and other things that we think are really effective therapy, this would be considered substantially more effective. If you don't believe the evidence then it's more effective or as effective, but if you really believe the evidence, I would go for substantially more effective.
DR. DAVIS: Are there any other categories anybody else would like to support? Because if not, there are two suggestions, and rather than following strict parliamentary procedure and voting the first motion up or down, I think I would like to depart from that to help us more efficiently make a decision as a committee, and just vote either for more

effective or substantially more effective. Is there any objection to that? If not, let's do that. So, is it Wade's turn?
DR. AUBRY: More effective.
DR. REDBERG: Abstain.
DR. GOODMAN: More effective.
DR. PIPER: More effective.
DR. WALLACE: More effective.
DR. CURTIS: More effective.
DR. MATUSZEWSKI: More effective.
MS. BARTLETT FOOTE: More effective.
DR. BROOK: Substantially more.
DR. McNEIL: Abstain.
DR. DAVIS: Seven for more effective, one for substantially more effective, and two abstentions.
We are done with the voting questions.
DR. PIPER: Question. Can we add any comment to that last voting question?
DR. DAVIS: Sure, proceed. I mean, we have these three discussion questions that we're going to try to discuss in the next few minutes, so if it's quick --
DR. PHURROUGH: Let me -- the discussion questions were out there for you to give us some

general advice, we don't have time to do that, I think we can skip those. If there's some parting comments that you would like to add to what you just voted on, we would be happy to hear those, so why don't we end with that.
DR. DAVIS: That's fine. I have on my watch 20 after three. Maybe we can take five minutes for any kind of additional commentary that somebody would like to make, and that will allow five minutes for closing remarks by CMS. So Margaret, proceed please.
DR. PIPER: I just wanted to say that despite some methodologic questions and analyses, I voted for more benefit because the analysis did convince me there was more benefit than not doing anything. However, I would have to say that I'm not sure there is very much more benefit and that it lasts for very long, based on the data that I've seen. So in terms of a long-term benefit, I am far less convinced.
DR. DAVIS: Yes, Susan.
MS. BARTLETT FOOTE: I would like to recommend that CMS look very carefully at the conditions that they would put on. In many coverage decisions there are some hurdles that have to be met

by the physician in order to fall into the area of coverage, and I would say that size of lesion and evidence that there has been some progressive vision loss, I think Dr. Bressler said, you know, a follow-up visit, some steps that need to be taken before this be would be covered.
The other issue we did not address at all was the number of treatments and I know in other areas, excessive number of treatments that don't show any benefit have been a problem for CMS, so I think they might be wise to have some aspect of numbers of treatments that would be within the scope of the coverage.
DR. DAVIS: Karl, then Bob.
DR. MATUSZEWSKI: I have a question of Dr. Bressler and Dr. Azab, and I meant to ask it earlier but I wasn't close enough to give you a squeeze. Do you feel comfortable with the dosing of the therapy in terms of the dose of the drug, the dose of the light, the frequency of the diagnostic check, or is that something that you think is going to be evolving.
DR. BRESSLER: I'm very comfortable with the dosing so far because in the Phase I and II trial where we looked at some different doses, except for a

very very high light dose, three times what we used in all these trials, there seems to be a wide therapeutic index, in that it doesn't seem to cause an adverse effect on the retina immediately. When we tried a reduced fluence rate, a reduced light dose in that VIM trial that I described for smaller minimally classic lesions, it seemed to work okay. So I'm very comfortable with the dose we're using now and I think it would work about the same give the different light doses that someone might do if they measured things slightly incorrectly.

DR. MATUSZEWSKI: And the dose of the drug is appropriate at 6 milligrams.

DR. BRESSLER: Correct. We saw just similar effects as we went up to about 12 milligrams.

DR. DAVIS: Quick comments from Bob and Rita, and then we will probably have to cut it off.

DR. BROOK: I would like to make a comment on the record that CMS consider implementing this policy only if they get from the surgeons cooperation in maintaining a national database on macular degeneration, similar to what the cardiac surgeons have done with the CTS, and that they collect enough detailed clinical data so that as new therapies come down the pike, we will be able to have better

evidence and reach agreements faster about what affects this population. And I wish it could be done voluntarily, but I would suggest you think very hard about trying to change the way the policies are made for this kind of work, and I think there is a big opportunity to use this as a way of changing the way we learn about what works and doesn't work since controlled trials will never answer all the questions that we need to answer.

DR. DAVIS: Rita.

DR. REDBERG: I just wanted to make a comment that despite my concerns about what I consider to be the most meaningful health outcome, visual function, that I really wanted to thank all the presenters, and particularly Dr. Bressler, Dr. Azab and Dr. Stone, because I thought everyone really, though there was some new data, that everyone really did an excellent job of sharing everything that we could to help us address these issues.

DR. DAVIS: Wade, were you trying to get in there?

DR. AUBRY: I just wanted to briefly say that I agree with Susan Foote regarding identifying those patients who are most appropriate for this therapy, and I'm not sure whether CMS would do that

in a coverage decision if they decide to move forward with a coverage decision, but certainly in a decision memorandum, something about training and experience of the ophthalmologist and the patient indications, those patients which most clearly benefit from this treatment would be appropriate.

DR. DAVIS: Steve.

DR. GOODMAN: This is just really following up on Bob's point when he said that the database would be useful for future technologies. I think what's absolutely critical is to see if what has been seen in the trials here is actually achieved in the field, so I think the follow-up is needed not just for the future evaluation, and I know he knows this, but to see if what we suspect is true here is actually true, because I still think that the weight of evidence here is below the standard that FDA is using and that is often used. I don't think we are certain beyond a reasonable doubt here that this achieves, or at least I certainly am not, that this achieves more than a minimal increase. I am well above 50 percent but well below 95.

DR. DAVIS: Barbara.

DR. McNEIL: Well, just one final comment. I noticed Dr. Azab at the beginning said that he was

unable to change his slides, because -- is that what you said, CMS wouldn't allow you to change your slides, or wouldn't allow you to submit new slides to us?
DR. AZAB: No, no, they did not have anything to say about the slides. It's just because the slides had changed from what we submitted to you in August, we had a new printed hard copy for you so that you could follow it, and according to their procedures, all the material had to be submitted before. So no, the slides -- we have said everything we wanted to say, it was just we wanted to make it easier.
DR. McNEIL: So that was my point in that you did have new data, and Dr. Bressler --
DR. AZAB: I did not have actually any new data. Most of the data that I presented on the slides were not on your slides, but were in the briefing document that we submitted because there was much more information there, and also the lesion size manuscript that Dr. Bressler mentioned that was just published, actually than manuscript because it was already approved, we had put it in your package, but I realize it was a huge package.
DR. McNEIL: Okay.

DR. DAVIS: Just before I hand things over to Steve and Michelle to wrap things up, I wanted to echo Rita's comment and thank all of the presenters, to thank CMS staff for the huge amount of work that they did to get us ready for this meeting, and also members of the public who testified before us earlier today. Steve.

MS. ATKINSON: For more information, you may visit our web site at www.cms.hhs.gov/coverage. To conclude today's session, would someone move that this meeting be adjourned?

DR. REDBERG: I move for adjournment.

MS. ATKINSON: Does someone second this motion?

MS. BARTLETT FOOTE: Second.

MS. ATKINSON: Thank you everyone for your time and participation in today's meeting. Steve, do you have anything to say?

DR. PHURROUGH: Yes. Just to again thank the panel members. I know this was a very challenging and somewhat agonizing decision based on the information you had and we do appreciate your tame an effort in doing this. Thank you.

(Adjourned at 3:30 p.m.)