FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE

OPHTHALMIC DRUGS SUBCOMMITTEE

OF THE

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE

8:35 a.m.

Wednesday, November 17, 1999

Versailles Room
Holiday Inn
8120 Wisconsin Avenue

Bethesda, Maryland

ATTENDEES

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ATTENDEES (Continued)

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H. ANDREW STRONG, PH.D.
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ALSO PRESENT:

GEORGE T. BLANKENSHIP
ROBERT M. GRAY
CHARLES THOMPSON

C O N T E N T S

NDA 21-119 VISUDYNE
(verteporfin for injection, QLT PhotoTherapeutics, Inc.)
for Treatment of Age-related Macular Degeneration (AMD)
in Patients with Predominantly
Classic Subfoveal Choroidal Neovascularization

P R O C E E D I N G S

(8:35 a.m.)

DR. FONG: Good morning. I'm Donald Fong. I'm the Chair of the Ophthalmic Drugs Subcommittee of the Dermatologic and Ophthalmic Drugs Advisory Committee. I'd like to welcome you to our meeting this morning. We're going to be discussing new drug application 21-119, Visudyne, for treatment of age-related macular degeneration.

First of all, I'd like to go around the room and have everybody introduce themselves. Jack?

DR. CIOFFI: I'm Jack Cioffi from Devers Eye Institute in Portland, Oregon.

DR. SEDDON: Johanna Seddon from Harvard Medical School, Massachusetts Eye and Ear Infirmary, Associate Professor of Ophthalmology.

DR. HERNDON: Leon Herndon from Duke University Eye Center in Durham, North Carolina.

DR. FONG: Donald Fong. I'm with Kaiser Permanente Medical Center.

MS. RILEY: Tracy Riley. I'm the Executive Secretary for this committee.

DR. KILPATRICK: Jim Kilpatrick, your friendly

biostatistician, from the Medical College of Virginia.

(Laughter.)

DR. CHAMBERS: Wiley Chambers, Deputy Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products.

DR. MIDTHUN: Karen Midthun, Acting Division Director of the same division.

DR. FONG: Next Tracy Riley will read the conflict of interest statements.

MS. RILEY: Good morning.

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

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S. Code, section 208(b), full waivers have been granted to Dr. George Cioffi and Dr.

Donald Fong. A copy of these waiver statements may be obtained by submitting a written request to agency's Freedom of Information Office, room 12-A30 of the Parklawn Building.

In addition, we would like to disclose that Dr. Cioffi's employer, the Devers Eye Institute, has a financial interest in a firm which has a product that could potentially compete with Visudyne. Although this interest does not constitute a financial interest in the particular matter within the meaning of 18 U.S. Code 208, it could create the appearance of a conflict. However, in light of all relevant circumstances, the agency has determined that it is in the best interest of the government to permit Dr. Cioffi to participate fully in all matters concerning Visudyne.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon.

DR. FONG: Thank you, Tracy.

Wiley Chambers will make some comments.

DR. CHAMBERS: Thank you. We'd like to welcome everyone to this advisory subcommittee meeting.

The topic today is a pending new drug application. We will be discussing the clinical aspects of this application. We will not be dealing with any of the chemistry/manufacturing aspects. Everyone should bear in mind that new drug applications contain not only clinical information, but non-clinical information, chemistry, and manufacturing information, and all of that will need to be reviewed before any action is taken on the application. Even if everything was in the most favorable light and there were no issues raised in any aspect, that does not mean this product would be approved tomorrow. There are additional reviews ongoing. There are additional issues in the chemistry/manufacturing area which the agency will handle internally.

We are interested in the clinical expertise that is present at the table and interested in the comments regarding the clinical issues, and that will be the subject of the conversation today.

I thank you all in advance for you comments. Thank you.

DR. FONG: Next we have the open public hearing. I'd like to remind each speaker that they need to speak into the microphone because the information you speak about will be transcribed.

I believe George Blankenship will be speaking.

MR. BLANKENSHIP: Good morning. I'm G.T. Blankenship from Oklahoma City. I'm a lawyer by profession, although I haven't practiced for a number of years. I've been involved in private investments and banking. I'm in my 10th year as a regent at the University of Oklahoma.

I was discovered to have macular degeneration in August of this year. It came about as I had gone on an extended vacation and I started to have difficulty with my reading glasses. I had had cataract surgery about a year and a half earlier, and I was told by the surgeon that I had the beginnings of a cataract in the other eye and would, undoubtedly, have to do the same thing at some point. I naturally assumed that that's what this problem was.

So, I arranged for an appointment at the Dean Magee Eye Institute in Oklahoma City and went for my

examination. Much to my shock, in the doctor's opinion I had macular degeneration.

It is a very traumatic happening because I guess we would all say that sight is our most beloved sense and that the loss of it is a very emotional happening.

I didn't know exactly know what to do. At the time it was recommended that I enter a clinical trial that was immediately available because of the condition of the eye, and I had some reluctance because of some of the conditions that that required. So, I sought to seek a second opinion. I was very fortunate to be able to get an appointment with Dr. Bressler at Wilmer Eye Institute, whereupon he advised me that he thought that waiting several weeks until the Visudyne treatment would become available in my situation -- that the risk was worth the gain, which I accepted his advice and was treated with the Visudyne treatment.

It's a relatively simple process. The chemical is injected intravenously over a precise period of time, 10 minutes, at which time an additional 5-minute waiting period expires before they use a low powered laser to activate the properties of the chemical. It's very noninvasive. There is absolutely no pain. It's a very simple process.

That was in September. I will be treated again, or at least examined again and possibly treated, in December.

I would like to say that this treatment has in my case given me a great deal of hope. Macular degeneration is something that happens to someone else. Most people don't have an awareness of it. I am told that it affects millions of people in this country, but unless it happened to someone very close to you or to you yourself, there's very little awareness. And it is devastating from an emotional standpoint.

This treatment has given me a great deal of hope, hope that I can preserve the sight in my other eye, hope that, because of the nature of the treatment no permanent damage having been done, as with the earlier treatments with a more powerful laser, that something may come along that sight in this eye can be restored.

And lastly, I hope that this treatment will become available to others affected, as I have been, for the same reasons that I've already stated, that the psychological effect on me has been very, very positive.

I appreciate your time and my ability to come here and express these opinions. Thank you very much.

DR. FONG: George, before you go, also I wanted to remind all the other speakers, when they come on, please also disclose your relationship with the company, if you have any.

MR. BLANKENSHIP: I have none.

DR. FONG: Thank you, Mr. Blankenship.

The next speaker will be Charles Thompson. He is a radio broadcaster for WBAC radio and is an AMD patient who has not been treated with Visudyne.

MR. THOMPSON: Thank you very much, and good morning, ladies and gentlemen.

I have no interest. I have never heard of the company before, so this is brand new to me.

I understand my function here is to tell people how I came into this position of macular degeneration and what I did to try and help myself.

This goes back about two years, and I'm just driving in the morning one day and I'm on a two-lane road, and the boundaries of the roads are painted in yellow about 3 inches wide on each side. And all of a sudden, as I glanced to look at one on the left side of the road, that 3-inch span split right in the middle. There was a hole right down there.

There were two sides to it which was rather startling, and I thought, wow, what's going on? I didn't really know, and just as quickly as it came, it left. And I thought, well, I guess it's just a fluke of nature. I'm not going to be that concerned about it, and I did not run right in to have my eyes examined.

About two months later wintering in Florida, I recognized the fact that I had a problem. In my business, it's emphasized just a little bit. But the problems are these as I saw them in the sunshine of Florida. Looking across the road to the roof of my garage, it waved. Looking at the venetian blinds in my apartment, they were not straight, they were wavy. Everything had that wavy look to it. And I realized then that there was something wrong that I didn't realize, and I found out by coming back to Baltimore and going to the Wilmer Clinic to find out what this was all about.

I have been receiving treatment and it is kind of on a cycle. It seems that the capillaries and the vessels in my eye, after laser treatment, will be just fine, and the eye will be normal in almost all respects. Over a period of maybe 6 weeks or maybe sometimes a little bit more than that, then the waviness is there again.

Fortunately, Dr. Bressler anticipates that and sets my appointments up that way. So, I just go in about every two months or maybe a little bit more and have another treatment.

I have vision in the left eye, but I do not have the ability to read with my left eye. Thanks to the Wilmer Clinic, I still have the ability to read in my right eye.

When this condition was made known to me and the treatments started, I felt, after talking to the doctors at Wilmer, that one of the first things I had to do was to let my three children know that this could be hereditary. I called my son and my daughters to let them know that maybe sometime down the road this could happen to them. It didn't mean that it would happen to them. I understand that, but the possibility is there. So, I warned them in advance of what to look for. In that all three of my children do wear glasses, I said go in and make sure that you have a thorough examination, do it as you have an annual physical, if necessary, anything to protect yourself, anything to give the people who work to help me and my condition a chance to do their job. I was too late with the first eye, but I am on time and on schedule with Dr. Bressler with the second eye.

Even with this eye, what are some of the things that are difficult? Number one, reading a commercial. Difficult. In the commercial would be a simple, little word like "can't," c-a-n-'-t. My vision would let me see c-a-n, and I would miss the apostrophe and the t. That makes it awfully hard to read a commercial. So, I'm being taught to read again, so to speak, into a microphone, and believe me, it needs a lot of improvement. Of course, people say that about me for years, I need to improve.

(Laughter.)

MR. THOMPSON: And that's what we're trying to do.

But the things that happen that are so unusual. If I look at a red light, I can still see the red light, but instead of sitting up there in the socket that I'm accustomed to, it sits over here at 8 o'clock. I can still see the green without any trouble, the amber, and the red, but they're not in that case that holds the traffic light.

I'm a golfer and I went up to hit some golf balls Sunday afternoon. I put a half a dozen golf balls down on the green to put, and the first ball I putted, I tracked it nicely, and then suddenly it disappeared, and about 2 feet

close to the hole, I could see it again. So, when I play golf now, somebody has to stand behind me to tell me where the drive goes, and that gets some very interesting conversations started.

(Laughter.)

MR. THOMPSON: But I cannot see the ball in flight.

That means that the years I've spent doing baseball, it would be very difficult, unless I can improve this condition in my eye or take very, very good care of this condition in my eye, to track the line drive, the fly ball, the foul balls, and things of that sort.

I think being a layman and not understanding the problems that you in this room face, I hope I am not out of order in asking that you give as much consideration as possible to this new drug. I have heard about it. I am not eligible for that yet, but in talking to Mr. Blankenship, I understand how well it has worked and how much better my future could be if this drug were available.

Thank you very much.

DR. FONG: Thank you, Mr. Thompson.

The next speaker will be Robert Gray. Mr. Gray

is the CEO of the Foundation Fighting Blindness, an advocacy group with great interest in treatments for AMD and other ocular degenerative diseases.

MR. GRAY: Good morning. My name is Robert Gray, and I am the Chief Executive Officer of the Foundation Fighting Blindness. I'm grateful to have this opportunity to speak with you today about the urgent need to find treatments and cures for macular degeneration. I am here of my own volition and I am not being paid as a consultant by CIBA Vision or QLT and have received no compensation for being here today.

We have millions of Americans who are losing their sight to retinal degenerative diseases. Established in 1971, the Foundation Fighting Blindness has an urgent mission to develop effective treatments and cures for blinding retinal degenerative diseases, like macular degeneration, retinitis pigmentosa, and Usher's syndrome. Through its research centers and targeted programs, the foundation operates the largest nonprofit macular degeneration and retinal disease research program in the world. Since its inception, we've invested over $100 million on research.

We are extremely heartened to see companies like

QLT PhotoTherapeutics and CIBA Vision devoting considerable R&D efforts to blinding retinal degenerative diseases.

Ten years ago, researchers were still scratching their heads trying to understand what caused these diseases. Sight-saving treatments and cures seemed hopelessly out of reach, but what a difference a decade can make. Today several promising experimental treatments could soon emerge from clinical trials. There was a time not long ago when these diseases were little understood and funding support was nonexistent. This FDA hearing represents a real turning point in the fight against these diseases. As the Chief Executive Officer of the foundation, I hope to soon attend many more hearings like this one today.

Macular degeneration exceeds cataracts and glaucoma as the leading cause of vision loss in adults over age 55. This blinding disease currently steals the vision of more than 6 million Americans and another 9 million Americans exhibit pre-symptomatic signs of the disease. The incidence of the disease will further sky-rocket as baby boomers reach retirement age.

Numbers can only begin to lend a sense of this emerging public health crisis. Without sight-saving

treatments for macular degeneration, we will soon be faced with an aging population requiring massive public assistance programs. People in the twilight of their productive careers will be prematurely forced onto the rolls of an already overburdened Social Security system. An entire generation of Americans, completely dependent on the automobile, will be stripped of their driving privileges, placing great strain on nonexistent or inadequate public transportation systems. Unable to live independent lives, millions of otherwise healthy, older-age Americans will be institutionalized in expensive assisted living communities.

On a personal level, macular degeneration causes great emotional anguish and loss. Driving becomes a harrowing and dangerous excursion. Unable to drive, patients are imprisoned in their homes while trying vainly to maintain independence. For avid readers, gleaning even newspaper headlines turns into a frustrating exercise. Hobbies and skills that have been honed over a lifetime are no longer possible. The joy of watching a grandchild's face light up is missed. Tragically people with macular degeneration are forced to watch their central vision fade to black and are left to distinguish the vague images that enter their

peripheral vision.

Mr. Henry Gruenwald, a former U.S. Ambassador to Austria and Editor-in-Chief of Time Magazine, has openly and heroically shared his struggle with macular degeneration. In the Foundation Fighting Blindness' most recent annual report, Mr. Gruenwald shares that -- and I quote -- "After a lifetime during which reading and writing have been as natural and necessary as breathing, I now feel the visual equivalent of struggling for breath." In his recent published memoir called Twilight, Mr. Gruenwald relates the sometimes unbearable sorrow and depression that accompanies the loss of the visual world, a depression that became so acute that his wife forced him to seek professional help.

Unfortunately, Mr. Gruenwald's story is too common. Every day people call the Foundation Fighting Blindness desperate to hear about new treatments. There is a central theme to all of their calls. They want to know what we can do for them today. As the largest nongovernmental supporter of medical research, the foundation hopes that promising treatments like photodynamic therapy will soon become a reality.

Thank you very much for allowing me to address

the panel.

DR. FONG: Thank you, Mr. Gray.

Next the sponsor will present their new drug application.

MR. MANDT: Good morning. I'm Larry Mandt, Vice President of Regulatory Affairs for QLT. On behalf of the company and our co-development partner, CIBA Vision, I'd like to thank FDA for the timely opportunity to review our experience with verteporfin therapy.

We believe that verteporfin provides a clinically relevant benefit to many patients where no treatment has previously been effective. Over the course of the next hour, we intend to show the panel why this benefit is reasonable, appropriate, and warrants inclusion in the physicians' armamentarium.

Our presentations today are intended to highlight the key information in the briefing document before you. To that end, we prepared the following agenda.

Following my introduction, Dr. Philip Rosenfeld will review the background of AMD. Dr. Andrew Strong will summarize the phase I/II results. The phase III study design and efficacy results will be presented by Dr. Neil Bressler.

Dr. Mohammad Azab will present an overview of safety and review the risk/benefit assessment for verteporfin therapy. I will close with brief concluding remarks and facilitate answering any questions you may have.

In addition to the presenters, there are several experts with us today to answer questions. Dr. Lee Jampol, Professor of Ophthalmology at Northwestern University, is a member of the data safety monitoring committee for the phase III clinical trials. Dr. Yong Hao from QLT and Mr. John Koester from CIBA Vision have been responsible for the statistical analysis of the data from the verteporfin therapy clinical trials. Dr. Jean-Marie Houle from QLT has been involved in the pharmacokinetic and pharmacological evaluation of the therapy. And Dr. Al Reaves from CIBA Vision is responsible for ongoing clinical trials with verteporfin.

To provide some perspective, I'd like to briefly review the key regulatory events that led up to today's meeting. QLT filed an IND to evaluate the drug as a treatment for age-related macular degeneration in early 1995. The phase I/II clinical trial proposed in this IND was conducted and provided evidence of the basic safety and efficacy of verteporfin in controlling choroidal neovascularization.

At an end of phase II meeting held with the division in July of 1996, key points related to phase III clinical trials were agreed upon. The primary efficacy endpoint would be the proportion of patients with less than 15 letters vision loss at month 12. 12-month data to demonstrate safety and efficacy was adequate to support filing an NDA, and 24-month follow-up was necessary to determine long-term effects.

With these key agreements in place, we initiated phase III trials in December 1996, enrolled all patients in less than 1 year, and completed 1-year follow-up on September 25th, 1998.

It was with this data set that we proceeded with preparation of an NDA. The NDA and the supporting PMAs for the light delivery devices were filed on August 16th, 1999. Shortly thereafter, the NDA was designated for priority review by FDA.

Verteporfin therapy was submitted to FDA as a combination product consisting of three filing elements. The NDA for verteporfin for injection, the drug product. Please note that verteporfin for injection is intended to be marketed under the trade name of Visudyne. The other elements of the

filing were two PMAs for the light delivery devices used to activate the drug.

In addition to the U.S. filings, applications have been made in the European Union, Switzerland, Australia, New Zealand, Norway, Iceland, and Canada.

The U.S. NDA proposed the following indication for verteporfin therapy. Visudyne is indicated for the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

I would now like to turn the podium over to Dr. Philip Rosenfeld.

DR. ROSENFELD: Good morning. My name is Dr. Philip Rosenfeld. I am an Assistant Professor of Ophthalmology at the Bascom Palmer Eye Institute of the University of Miami School of Medicine. I've been a principal investigator in the phase III clinical trials using verteporfin therapy.

My role this morning is to provide you with background information on age-macular degeneration. In the next few minutes, I will describe how age-related macular degeneration affects the eyes and what this means to patients who have this visually debilitating disease. Then I will

describe the growing public health concern of age-related macular degeneration in our aging population. Finally, I will discuss the current treatment options for patients with age-related macular degeneration and the limitation of these therapies.

This slide depicts the normal anatomy of the eye with particular emphasis on the anatomy of the retina. The macula is a specialized portion of the retina responsible for fine, central visual acuity. The center part of the macula is known as the fovea and the fovea is responsible for the best central visual acuity. Central visual acuity is required for such things as reading, driving, and recognizing faces.

Age-related macular degeneration is a disease that affects the outer aspects of the retina and portions of the choroid. In particular, the layers of the retina primarily affected include the photoreceptors, the retinal pigment epithelium, Bruch's membrane, and the choroidal circulation. Bruch's membrane is a specialized collagenous layer that separates the choroidal circulation from the retinal pigment epithelium and photoreceptors.

The etiology of AMD is multi-factorial and complex and remains poorly understood. Although we do not

know the cause of this disease, we know how the disease appears and how the disease progresses.

The earliest detectable stage of AMD is the deposition of yellow spots under the retina known as drusen, as shown here in the fundus photograph. These drusen are representative of a diffuse thickening within Bruch's membrane. And remember, it's the Bruch's membrane that separates the choroidal circulation from the retina.

In the early stage of macular degeneration, severe vision loss is not seen. Central vision loss occurs in the late stage of age-related macular degeneration, and this stage can be divided up into two forms: the atrophic (dry) form or the neovascular (wet) form.

In the atrophic form of AMD, there is loss of photoreceptors, of retinal pigment epithelium, and choroidal circulation within the macula. This loss of tissue can take decades to evolve, and this form of late AMD is responsible for only a minority of cases with severe vision loss.

The most severe vision loss in AMD occurs from the neovascular form of the disease. In this stage, blood vessels grow from the choroidal circulation through Bruch's membrane and under the retina. These abnormal new blood

vessels leak fluid and protein and blood and fibrous tissue is deposited. The combination of these blood vessels and fibrous tissue results in scarring of the macula, destruction of the photoreceptors, and loss of central vision.

This loss of central vision can occur within 3 to 24 months after the development of these blood vessels.

Neovascular AMD is responsible for the vast majority of cases of severe vision loss from this disease.

As these new blood vessels begin to grow and leak under the retina, the patients appreciate a visual distortion that could be seen here on the left-hand image or what should be a normal grid. As the disease progresses, the central vision is lost, and when the patient looks, they see a black area surrounded by distorted blurred vision. With this vision, they're unable to recognize faces and read words, and even normal activities that we take for granted are severely affected.

These abnormal blood vessels can be recognized using a technique known as fluorescein angiography. This technique involves the injection of a dye known as fluorescein followed by specialized photographs of the macula. Not only can we identify where these blood vessels are located, but we

can also distinguish the type of blood vessels and classify them into one of two forms. The slide on the left depicts a lesion that has a classic neovascular component. This classic neovascularization is characterized by lacy, early hyperfluorescence with brisk leakage of fluorescein throughout the angiogram.

The image on the right shows a lesion with three components. These components are occult neovascularization, classic neovascularization, and blocked fluorescence, which in this case represents blood. The occult neovascularization is characterized by a stipple type of fluorescence with minimal leakage of fluorescein during the course of the angiogram. The classic neovascularization can be seen here as brighter fluorescence, and it is this form of neovascularization which has been shown in clinical studies to be associated with the more rapid vision loss in most average situations.

Neovascular age-related macular degeneration is the leading cause of blindness in individuals older than the age of 50 and the prevalence increases dramatically with age. The neovascular form of AMD can develop in one or both eyes of up to 200,000 U.S. citizens every year, and most eyes affected will experience vision loss within 2 years of onset. With an

aging population, neovascular AMD is becoming an increasing public health problem.

The only accepted treatment for neovascular AMD at this time is thermal laser photocoagulation. Several studies have shown that laser photocoagulation is useful in selected cases of neovascular AMD. The benefits and limits of laser photocoagulation can be appreciated from the results of the macular photocoagulation study that can be seen on the next slide.

This slide depicts the 3-month and 24-month follow-up from the Macular Photocoagulation Study Group's evaluation of subfoveal choroidal neovascularization. They were able to show some benefit in certain lesions. This graph depicts the average visual acuity loss from baseline in a group that was treated with laser and a group that was randomized to observation alone. At 3 months, the laser treated group has lost significantly more vision than the observation group. This vision loss at 3 months is the vision loss that occurred immediately at the time of laser photocoagulation. The benefit of laser therapy is only realized by 18 months, and by 24 months, the vision loss experienced by the control group is significantly more than

the vision loss experienced by the laser group.

This graph depicts two very important points. First, after laser photocoagulation, there is an immediate loss of central vision, and second, if left untreated, neovascular AMD will result in continued vision loss.

Due to the limitations of thermal laser photocoagulation, additional therapies are now being investigated for neovascular AMD. Photodynamic therapy with verteporfin will be discussed today, and there are other photosensitizing agents that are also under investigation. Submacular surgery is now being studied in a multi-center, randomized clinical trial sponsored by the National Eye Institute. In addition, a number of clinical trials are underway evaluating the radiation therapy, as well as anti-angiogenic agents for neovascular age-related macular degeneration.

So, in summary, neovascular AMD is the primary cause of severe, irreversible vision loss in patients over age 50, and the prevalence of the disease increases dramatically with age. It is a major problem and a growing public health concern, particularly among our aging population. And there is no treatment currently available for the vast majority of

patients with neovascular AMD, vision loss secondary to choroidal neovascularization.

I would now like to turn the presentation over to Dr. Andrew Strong.

DR. STRONG: Good morning. My name is Andrew Strong, and I'm responsible for the ophthalmic clinical programs at QLT PhotoTherapeutics.

The topics I'll cover include, firstly, the mechanism of action of verteporfin therapy. Then I will give a brief summary of the main results of our phase I/II studies which provided the rationale for the phase III regimen, including the drug and light dose and the retreatment interval.

Verteporfin therapy is a two-step process consisting of drug and light treatment. The drug verteporfin is a photosensitizer. In other words, it is a light-activated drug. The first step is the intravenous injection of verteporfin, after which it is preferentially retained in the proliferative new blood vessels relative to the normal blood vessels. Verteporfin has been shown to be retained in the choroidal neovascular membrane.

Verteporfin is inactive without light, so the

second step involves light activation of verteporfin by shining nonthermal laser light at the neovascular lesion via a slit lamp and a contact lens.

When verteporfin is activated by light, it reacts with oxygen producing reactive singlet oxygen and other free radicals locally. These free radicals damage the endothelial cells, ultimately resulting in localized vascular occlusion of the CNV. It is believed that this selective damage of leaking blood vessels results in stabilization of vision or reduction in the rate of vision decline.

So, verteporfin therapy provides a dual selectivity for the choroidal neovascularization, firstly, by its selective retention in the tissue and, secondly, by shining the light only on the area where the treatment effect is required.

On the basis of this mechanism of action and preclinical studies, a phase I/II clinical study was initiated in 1995, study OCR001 was an open-label, non-randomized, non-controlled study at four centers. The study included a total of 142 patients, of whom 128 had AMD. The objective of the study was to establish safety and efficacy in controlling leakage from CNV. The study was later expanded to evaluate

different dosing parameters and to identify a maximum tolerated dose, or MTD.

The primary assessment of efficacy was based on the extent of fluorescein leakage from CNV. Visual acuity was used as a secondary assessment of efficacy, as well as being the most important parameter for assessing ocular safety. Patients underwent assessments within 1 week before treatment and 1, 4, and 12 weeks after treatment.

This slide shows a representative fluorescein angiogram of a CNV lesion from this study with extensive leakage of fluorescein at baseline, shown by this central area of hyperfluorescence.

1 week after treatment, there is complete absence of leakage from the CNV, while the perfusion of overlying retinal vessels that had been irradiated with light was unaffected. This effect was not associated with vision loss. In fact, on average in all patients treated in the study, the visual acuity had improved by nearly 1 line at this time point.

However, by 4 to 12 weeks after treatment, some leakage again can be seen, although covering an area smaller than that seen at pretreatment.

We evaluated a large number of treatment regimens and varied both the drug and light parameters, but we were unable to prevent this pattern of leakage in most, but not all cases. We found that if the light dose was increased to high, non-selective damage occurred to the retinal vessels. On the right-hand photograph, one can see there is no perfusion of retinal vessels in the area that received light treatment. This occurred in 3 out of 14 patients, with the highest light dose of 150 Joules per centimeter squared. No non-selective events like this occurred at any light dose less than 150 Joules per centimeter squared. So, the maximum tolerated light dose was 100 Joules per centimeter squared.

CNV leakage, therefore, occurred in most patients after 4 to 12 weeks after a single treatment course in all the regimens we tested. Since increasing the light dose was not possible, multiple treatments were attempted at intervals of 2 to 12 weeks in 42 patients. Most of them received retreatments at intervals of 4 weeks. However, CNV leakage still recurred 4 to 12 weeks after retreatment in most of the patients. Importantly though, leakage could be stopped after each retreatment without impairing visual acuity over the 12 weeks of follow-up.

Based on the phase I/II data, our rationale for the phase III regimen chosen was to use the minimum effective dose of both verteporfin and light that caused complete closure of classic CNV 1 week after treatment. The regimen was also associated with the lowest percentage of lesions with classic CNV progression beyond the borders of the original lesion by 12 weeks. Also, the chosen regimen had the most favorable mean changes in visual acuity from baseline.

Our rationale for a reassessment and retreatment interval was that CNV recurred and continued to grow in most lesions, suggesting that if retreatment was not administered, further growth and macular destruction would occur. 3 months was chosen as the retreatment interval because in most lesions the area of leakage was still confined within the borders of the lesion that was seen at baseline.

Importantly, retreatment at that time was able to safely reclosure the leaking CNV. 3 months was, therefore, considered to be an appropriate interval for the phase III program. It's also important to note that retreatment at shorter intervals did not appear to enhance efficacy.

As a result, the regimen chosen for phase III consisted of a verteporfin dose of 6 milligrams per meter

squared of body surface area, given as an intravenous infusion over 10 minutes. The light dose was 50 Joules of energy per centimeter squared of target tissue applied at 15 minutes after the start of the infusion. This was the minimum light dose with proven efficacy. The maximum tolerated dose of light in the trial was 100 Joules per centimeter squared and non-selective events were seen at 150 Joules per centimeter squared, which was three times the light dose we've chosen. The retreatment interval was 3 months if CNV leakage was detected by fluorescein angiography.

So, in summary, verteporfin therapy is a two-step process involving systemic intravenous administration of verteporfin, followed by light application to activate the drug. Activation of verteporfin results in endothelial cell damage and CNV closure without harmful effects on the normal retina.

Our phase I/II program has demonstrated that CNV leakage and lesion growth can be contained for up to 12 weeks without short-term adverse effects on visual acuity. However, CNV leakage recurred in most patients, requiring multiple treatments at 3 monthly intervals.

Evaluation of dosing parameters, therefore,

provided the rationale for an appropriate regimen to be tested in our phase III program.

I'll now ask Dr. Neil Bressler to continue the presentation of the phase III study.

DR. BRESSLER: Good morning. I'm Dr. Neil Bressler. I'm a Professor of Ophthalmology at the Wilmer Institute of the Johns Hopkins University School of Medicine. In addition, I've spent over a decade designing and directing randomized clinical trials evaluating treatments for age-related macular degeneration.

Today, on behalf of our investigators and as Chairman of the Study Advisory Group, which oversees the scientific protocol for this investigation, I'll present to you the study design and the results of the phase III program for this verteporfin therapy.

The topics that I will cover will include the objectives and design of the phase III studies, the pertinent baseline characteristics of the patients enrolled in these studies, the follow-up that was obtained, and the vision and angiographic outcomes that proved the efficacy of this therapy.

The main objective of the phase III program was

to determine if verteporfin therapy in patients who have subfoveal choroidal neovascularization secondary to AMD would safely reduce the risk of vision loss compared to a placebo given as a sham treatment.

The studies were randomized, placebo-controlled, and double-masked clinical trials. Patients had a screening visit to assess eligibility. If they were eligible to participate, they were randomly assigned to verteporfin or placebo therapy within 7 days of all their baseline assessments. Two-thirds of the patients then were randomized to verteporfin, and one-third of the patients were randomized to a placebo therapy.

The randomization was stratified by center to ensure a 2 to 1 randomization at each center. The randomization also was stratified by baseline visual acuity into two strata, approximately 20/40 to 20/80 and approximately 20/100 to 20/200, since baseline visual acuity was believed, at the time that the study was designed, to possibly have an impact on the visual outcomes.

Two trials were identically designed to assess reproducibility of the results and were numbered OCR002 study A and study B. These trials are known collectively by the

scientific community as the TAP investigation.

The studies were designed to allow for follow-up and treatment for up to 24 months. However, the primary analysis was prospectively designed to be performed after all patients had completed a minimum of 12 months of follow-up.

We then had a total of 22 centers, 11 in the United States, 2 in Canada, and 9 in Europe, that participated in the two studies.

The main eligibility criteria included patients who had age-related macular degeneration that was defined as having drusen or abnormalities of the retinal pigment epithelium that were consistent with AMD in patients who were no younger than 50 years of age.

All patients had to have a best-corrected visual acuity on an ETDRS chart of 73 to 34 letters, approximately 20/40 to 20/200.

They all had to have a fluorescein angiogram with subfoveal choroidal neovascularization that included evidence of classic neovascularization, although occult neovascularization could be present. All lesions had to have a greatest linear dimension no greater than 5400 microns on the retina.

And all patients had to have an ability to return for up to 2 years of follow-up.

Only one eye per patient could be enrolled and treated in the study.

Thus, this study was designed to assess verteporfin therapy in classic containing neovascularization that extended under the fovea.

The verteporfin group were given a verteporfin dose of 6 milligrams per meter squared of body surface area, diluted in dextrose 5 percent, while the control group was only given dextrose 5 percent as a placebo. All the patients then received an intravenous infusion of 30 milliliters over 10 minutes. The intravenous tubing was wrapped in foil to prevent the patient and treating ophthalmologist from knowing whether the patient was receiving verteporfin or the placebo.

The light using a diode laser was applied to all of the patients then 15 minutes after the start of this infusion, which was set at a wavelength of 689 nanometers. The light was set at an intensity of 600 milliwatts per centimeter squared given over 83 seconds, resulting then in a total light dose of 50 Joules per centimeter squared at the target lesion. This is about 1,000 times less than the light

intensity used for typical thermal laser photocoagulation. The light was produced by a diode laser that was specifically designed for this application, using a fiber optic that delivered the light through a standard slit lamp.

The spot size of the light used to activate the verteporfin was calculated by measuring the greatest linear dimension of the lesion, shown here by the dotted line, on a fluorescein angiogram and then adding 1,000 microns to ensure that a sufficient margin would cover the entire lesion, as shown by the spot size in the white circle on this slide.

2 to 4 days after each treatment, the patient was telephoned and asked standard questions that would elicit any systemic or ocular adverse events. The patients then returned to the clinic every 3 months, at which time they again underwent all of the procedures shown on this slide. If there was any evidence of leakage from classic or occult neovascularization or both on fluorescein angiography at that follow-up visit, then the patients were retreated with either verteporfin or placebo according to whatever they were assigned at their baseline randomization.

The prospectively defined primary efficacy endpoint was the percent of responders. The responders were

defined then as the proportion of patients who lost less than 15 letters of visual acuity on the ETDRS chart at the month 12 examination compared to baseline.

This is a photograph of the ETDRS vision chart that was used in the study. You can see that there are 5 letters per line, and every 3 lines, the size of the letters doubles, representing a doubling of the visual angle that the letters actually subtend on the retina. A loss of 15 letters, which can be equivalent to 3 lines on this chart, would take a patient, for example, from 20/40 to 20/80 or from 20/100 to 20/200, which could be the difference between being able to read or not read with magnification aids. Experts agree that a loss of 3 lines or worse represents a clinically relevant vision change with respect to the visual function of a patient.

A large number of secondary efficacy endpoints on visual outcomes shown here were planned to look for consistency in any treatment benefit that was suggested by the primary efficacy endpoint. And I'll review each of these in the results section.

In addition, there were several fluorescein angiographic outcomes that were planned to determine if there

were objective features on angiography that could confirm any visual acuity benefit, including how large the neovascular lesion became over time and whether leakage from classic or occult neovascularization persisted.

The primary analysis was an intent-to-treat analysis, using all randomized patients within the group to which they were randomized. Missing values were imputed using the last observation carried forward.

A confirmatory analysis was done on a group of patients defined as evaluable patients. This data set excluded patients for gross violations of either the inclusion criteria or the treatment protocol and did not use data imputation for missing values.

Prior to starting the study, there was a training and certification program for all treating ophthalmologists to confirm that they understood the eligibility criteria and the treatment protocol. Training and certification was also provided to the vision examiners, since visual acuity was the primary endpoint. The photographers, clinic coordinators, and sponsor monitors also received training, and the photograph reading center graders were trained to ensure reproducible assessment of the lesion characteristics both at baseline and

at follow-up.

Everyone except the person assigned to prepare and administer the infusion was masked. The unmasked individual who did the infusion was not involved in any patient assessments and was trained to ensure that all other team members remained masked.

An independent data and safety monitoring committee, chaired by Dr. Roy Beck, and including a statistician, retinal specialists, and clinical trial specialists, reviewed unmasked data at 6 monthly intervals in closed sessions to protect the patients' interests and to make sure that no safety concerns arose. The data and safety monitoring committee did not raise any safety concerns and did not recommend any changes to the protocol during the conduct of the studies.

In addition, a central unmasked photograph reading center at the Wilmer Institute at Johns Hopkins, with extensive experience evaluating angiograms in age-related macular degeneration, including two NIH-sponsored trials, reviewed fundus photographs and fluorescein angiograms from the baseline and at every 3-month follow-up visit.

A total of 609 patients then were randomized to

treatment in the two studies. There were 402 to verteporfin and 207 to placebo. Patient follow-up was excellent and almost identical in both study A and study B. Approximately 94 percent of both treatment groups completed the month 12 follow-up visit, which was judged to be excellent considering that the average age of the patients participating in this trial was 75.

With respect to baseline characteristics, there was a statistically significant difference with more women assigned to placebo. There also were more past or current smokers assigned to verteporfin, and there were more lesions considered by the reading center to contain blood in the placebo group.

This slide shows the percentage of patients treated at each visit. At the initial visit, all patients randomized received treatment. The percentage of patients retreated with verteporfin was always lower through follow-up than the patients that were retreated with placebo. These are not protocol deviations, not receiving retreatment. They are usually patients who did not have leakage at their follow-up assessment and therefore did not require retreatment.

It's also important to note that the percentage

of patients receiving retreatment with verteporfin decreased with each visit, with about 90 percent receiving treatment at month 3, 80 percent at month 6, 70 percent at month 9, and only 64 percent at month 12. This trend suggests that the need for retreatments likely will not go on indefinitely.

One of the issues raised by the FDA was that lesions demonstrate leakage within 3 months after treatment, but this data shows that fewer and fewer cases show leakage with longer and longer follow-ups.

I'll now show you the results of the primary efficacy endpoint for each of the studies, study A and study B, and then the combined studies, and all of this based on the intent-to-treat analysis.

The primary efficacy variable, the responder rate, which was defined as the proportion of patients who lost less than 15 letters from baseline is shown here for study A. At each follow-up visit, the proportion of patients who lost less than 15 letters was greater in the verteporfin group, starting at month 3, and at the planned primary analysis at month 12, the percent of responders in the verteporfin group was statistically significantly greater than in the placebo group, with a p value of .018.

In study B, on this slide, the primary efficacy results were highly consistent with those in study A, with a statistically significant difference of 16 percent in favor of verteporfin treatment at the planned primary analysis at month 12, the p value being .01.

The two studies, study A and study B, then achieved replication of statistically significant results of the primary efficacy endpoint based on the intent-to-treat analysis.

For the combined data, study A and B, the overall difference on this slide at 12 months was 15 percent in favor of verteporfin treatment, again with a p value less than .001.

As mentioned earlier, these analyses were based on an intent-to-treat data set, using the last observation carried forward to impute for missing values. As was prospectively planned in the analysis, the robustness of these findings were assessed by a confirmatory analysis using an evaluable patient data set with no data imputation that excluded either the rare gross violation of eligibility criteria or of the treatment protocol. This evaluable data set results, shown on this slide, were highly consistent across the two studies and consistent with the results

obtained from the primary intent-to-treat analysis. Since the two studies showed consistent efficacy data, the remainder of the presentation will use combined data from the two studies, A and B, but using the intent-to-treat analysis throughout.

All of the secondary efficacy vision and angiographic outcomes that were prospectively defined were statistically significantly better in the verteporfin treated group as shown on this slide. This was true for severe vision loss, time to moderate or severe vision loss, mean visual acuity change from baseline, mean contrast sensitivity change from baseline, and angiographic outcomes.

I'd like to review two important secondary efficacy endpoints that were based on angiographic outcomes, mainly the lesion size and the extent of neovascular leakage at follow-up.

At baseline, the distribution of the lesion sizes were well balanced between the two study groups, but by month 12, as you can see from this bar chart, the verteporfin group had a higher percentage of small lesions, less than 3 disc areas, or between 3 and 6 disc areas, while the placebo group had a higher percentage of large lesions, greater than 6 and greater than 9 disc areas. This statistically significant

difference in favor of verteporfin provided clear evidence that verteporfin therapy reduced the risk of lesion growth.

Another angiographic outcome measured was the extent of classic neovascular leakage at follow-up examinations, and I'll focus on two of the important categories, progression of classic neovascularization and absence of classic neovascular leakage. Progression of classic neovascularization is defined as evidence of classic neovascularization at follow-up that is beyond the area of the neovascular lesion noted at baseline. Absence of neovascular leakage was defined as no leakage of classic neovascularization at follow-up either within the area of the lesion noted at baseline or beyond this area.

As you can see from this bar chart, there was a higher percentage of progression of classic neovascularization in placebo patients at 12 months, while the verteporfin patients showed a higher percentage of absence of leakage at the 12-month examination. Again, these results were statistically significant at a p value of less than .001.

The primary efficacy endpoint, less than 15 letters lost at the month 12 examination, was then analyzed in a variety of prospectively defined subgroups of patients that

might possibly affect the treatment benefit, such as age, gender, visual acuity, lesion size, and composition of the lesion at the baseline examination.

Caution must always be used in interpreting these univariate subgroups. For one thing, this subgroup analysis only used the primary efficacy endpoint, which is a categorical endpoint. In addition, only the visual acuity was stratified at baseline. Although most important baseline characteristics were well balanced in the total population, there always is a potential for important baseline factors to become unbalanced in other subgroups. Moreover, sample sizes may be inadequate to detect statistical significance despite treatment effects sometimes being apparent in subgroup analyses.

So, looking at these subgroups, first the baseline visual acuity. This was prospectively stratified into two subgroups of 73 to 54 letters, which is approximately 20/40 to 20/80, and 53 to 34 letters, approximately 20/100 to 20/200. In both subgroups, there were significantly more verteporfin treated patients who lost less than 15 letters compared to baseline by the month 12 visit.

For age, we divided the patients into those under

75 and those 75 and older. In both subgroups, the verteporfin treated patients had a better outcome than the placebo treated patients. Now, although the younger subgroup had a greater treatment benefit than those in the older subgroup, the test of interaction was not statistically significant. In other words, the difference in the treatment benefit for the younger versus the older group was not statistically significantly different.

In subgroups by gender, the treatment benefit was apparent in both women and men. It's of interest to note that in the placebo treated subgroups, women tended to have a greater number of responders than men. This trend may have worked against a treatment effect in the overall population since there were significantly more women assigned to placebo.

Dark and light irides both had a treatment benefit. Although the light irides had a slightly larger benefit, again the test of interaction was not statistically significant.

The greatest linear dimensions of the lesions were grouped based on the diameter of different disc area circles. We prospectively categorized the lesions' greatest linear dimensions into four groups: less than the diameter of

a 3 disc area circle, between 3 and 6, between 6 and 9, and in a few cases greater than 9. All categories of lesion size demonstrated a treatment benefit and there was no trend for smaller or larger lesions benefiting more or less.

To understand the lesion component subgroups by classic neovascularization, this slide illustrates the three different subgroups that were graded by the photograph reading center from the baseline fluorescein angiogram with respect to the percentage of the lesion which was classic neovascularization. For this lesion on the left, the area of classic neovascularization shown here is 50 percent or more than the area of the entire lesion, which in this lesion is all of classic and occult neovascularization and blood. I'll remind you that these are the lesions for which approval is being approved that we've termed predominantly classic neovascularization.

Now, for this lesion in the middle, the area of classic neovascularization is more than 0 percent but less than 50 percent of the entire lesion. And this lesion on the right has no classic neovascularization. As a reminder, one of the inclusion criteria was that lesions were required to have evidence of classic neovascularization as demonstrated on

the middle and left sketches here. So, if the reading center graded a lesion in which classic neovascularization was 0 percent, like on this right panel, it was a case in which the enrolling ophthalmologist must have thought there was some classic neovascularization that was not recognized by the reading center grader. And this occurred in 9 percent of the patients.

On the next slide, I'll show you the primary efficacy results by these three categories. The predominantly classic neovascular subgroup had a large benefit, judged by our investigators to be quite clinically relevant as there was an absolute difference of 28 percent more verteporfin patients losing less than 15 letters at the month 12 examination. For the subgroup in which the area of classic neovascularization was more than 0 but less than 50 percent of the entire lesion, the responder rate was similar for the two groups. However, it's worth noting that other secondary endpoints such as contrast sensitivity and angiographic outcomes showed a treatment benefit in this subgroup.

Interestingly, this subgroup with no classic neovascularization at baseline had a large treatment benefit with a 33 percent higher responder rate in verteporfin

patients. However, the number of the patients in this subgroup was small and, as I mentioned earlier, these lesions did not meet all eligibility criteria as judged by the photograph reading center. We would prefer to reserve judgment on the effect of verteporfin therapy on these lesion types until we have results from a study evaluating these cases with no classic neovascularization in greater detail, which is in an ongoing phase IIIb program.

We also looked at the outcome in a subgroup analysis by the absence or presence of occult neovascularization, as graded by the photograph reading center from the baseline fluorescein angiogram.

For this lesion on the left, the lesion has no occult neovascularization. There is only classic neovascularization and blood.

For this lesion on the right, the lesion does have occult neovascularization. I would emphasize, though, that for these lesions that are sketched on the right, they were a very heterogeneous group in whom more than three-quarters had an area where the classic neovascularization was less than 50 percent of the entire lesion.

When we looked at the outcome then in a subgroup

analysis by the absence or presence of occult neovascularization, you can see that most of the treatment benefit was again found in lesions which contained no occult neovascularization. Again, I'll remind you that in a group of lesions with occult neovascularization in this subgroup, more than three-quarters of the patients had an area of classic neovascularization which was less than 50 percent of the area of the entire lesion, impacting on the smaller treatment benefit you see here, compared to the large treatment benefit noted for predominantly classic lesions that I showed two slides earlier.

In all of these subgroups then, the verteporfin treated group had a numerically higher responder rate, although statistical significance was not always achieved. So, based on these univariate analyses, it appears that several factors could affect treatment outcome, including lesion component and possibly patient age, gender and iris color.

With so many variables potentially having an effect on the treatment outcome, we conducted a multivariable logistic regression analysis to correct for factors that might affect outcome and that may have been imbalanced between

treatment groups at baseline. Only lesion component showed a statistically significant interaction with treatment in this analysis. Age, gender, and iris color had no significant interaction.

As a result of the subgroup analyses and multivariable analyses, the study group concluded that most of the visual acuity benefit with verteporfin observed in the overall study could be attributed to the subgroup of patients with predominantly classic neovascular lesions. Therefore, the sponsors, the TAP study group, and the data safety and monitoring committee proposed that the indication for verteporfin therapy initially be for this subgroup. Ophthalmologists who are comfortable and experienced in the interpretation of neovascularization in AMD using fluorescein angiography should be able to readily identify these predominantly classic lesions.

Another issue raised by the FDA is the discrepancy between interpretation by the reading center and the treatment center. With respect to interpretation at baseline, there were only a few discrepancies in interpretation, and on review of these cases with the investigators, the study group agreed that most of the

discrepancies were near misses.

For example, a lesion in which the photograph reading center interpreted a lesion that had a greatest linear dimension of greater than 5400 microns may have been interpreted by the treating ophthalmologist as being just slightly less than 5400 microns, and this occurred in from 4 to 6 percent of the patients enrolled in the trials.

Since the indication proposed at this time is for predominantly classic neovascular lesions, I think it's important to present the efficacy results which I'll show for this subgroup on the next few slides.

For the primary efficacy endpoint in this subgroup, there was a significant benefit seen by the very first follow-up visit at month 3 which then had grown by the month 12 exam, with approximately two-thirds of the verteporfin patients at that time point versus a little more than one-third of the placebo patients losing less than 15 letters. This difference of 28 percent, as mentioned earlier, was statistically significant.

All secondary vision and angiographic outcomes for the predominantly classic subgroup were statistically significantly better in the verteporfin treated group, as

shown throughout this slide.

Looking at the mean change from baseline in visual acuity, the treatment benefit again was apparent at the first follow-up visit, and this treatment benefit had doubled by the month 12 visit. The mean difference at the month 12 visit was 11 letters. So, although verteporfin treated patients lost on average of 10 letters, placebo treated patients on average lost twice as much vision.

One of the issues raised by the FDA was that all patients seem to continue to lose best-corrected visual acuity. However, these are average visual acuity changes. If you look at the numbers behind these average changes in more detail, you can see that not everyone lost vision, especially in the verteporfin treated group shown in green here. This bar chart shows the overall distribution of change in visual acuity score from baseline at the month 12 exam. Almost 40 percent of the verteporfin group had stable or improved vision while the placebo group was associated with a greater proportion of cases with vision loss. The verteporfin treated patients then not only had a greater chance of avoiding moderate or severe vision loss, they also had a greater chance of maintaining stable or improved visual acuity by the month

12 examination.

Similarly, the treatment benefit in mean change from baseline in contrast sensitivity as determined by the number of letters read on a Pelli-Robson chart was apparent at the first follow-up visit. This difference of 5 letters in favor of treatment at the month 12 follow-up visit represents almost two segments on the Pelli-Robson chart where every 3 letters on this chart represents a segment or change in contrast sensitivity. So, 6 letters, or two segments, represents a 2 log rank change in contrast. A two segment change, for example, being able to read a letter at this contrast and then losing vision over time so that only letters at this contrast or more could be read represents a clinically relevant difference.

For example, a patient who can read these letters with 20/200 vision and better contrast sensitivity can perceive faces and signs and written words better than a patient with 20/200 vision who requires more contrast sensitivity and can only read these letters. Thus, the difference in contrast sensitivity is considered beneficial to visual function.

Finally, I'd like to address what data we have

that is relevant to considering bilateral treatment. This situation will come up since some patients will be receiving therapy for one eye and then subsequently develop a neovascular lesion in their other eye. Physicians will want to treat both eyes in this situation, so it's important to review what data is available regarding the safety and efficacy of this approach.

In OCR001, we noted that a similar angiographic effect was noted whether light was applied at 15 or 20 minutes post infusion. In addition, in OCR002 we saw similar outcomes and safety in the 18 patients that received light application 18 to 25 minutes after the start of the infusion instead of 15 minutes after the start of the infusion. So, if in a bilateral treatment we are activating the drug in one eye at 15 minutes and then in the second eye at 18 or 19 minutes, I expect the photodynamic effect in each eye to be similar to what was seen for the cases in the TAP investigation.

The feasibility of this approach and its safety are being explored further in OCR002 extension in which patients in this situation, who might require bilateral treatment, can indeed receive bilateral treatment.

In summary then, for the overall population in

the TAP investigation, both study A and study B, a statistically significant benefit was demonstrated in each study for the primary efficacy endpoint. Consistent with the primary outcome, all secondary efficacy outcomes, including other vision outcomes and angiographic outcomes, were statistically significantly better in the verteporfin treated patients. The angiographic benefits provided an independent outcome that suggests a potential mechanism to explain the vision benefits that were observed, specifically verteporfin therapy appeared to confine lesion growth and inhibit progression of classic neovascularization, resulting then in preservation of vision.

Subgroup and multivariable analyses demonstrated a significant lesion component by treatment interaction, strongly suggesting that lesions in which the area of classic neovascularization was 50 percent or more of the area of the entire lesion had the greatest treatment benefit. In this subgroup, there was a 28 percent higher responder rate at 1 year. Also at that time the verteporfin group on average had 2 lines better vision and on average had almost 2 segments better of contrast sensitivity.

I'd like to now turn the presentation over to Dr.

Mohammad Azab.

DR. AZAB: Good morning. My name is Mohammad Azab and I work in clinical research at QLT PhotoTherapeutics.

In the next few minutes, I will cover data on exposure to verteporfin treatment throughout the clinical development program. I would also cover the safety assessments that were conducted in the clinical trials. Then I will focus on the safety results obtained from the pivotal phase III trials, study A and B. Based on the efficacy data that you just heard from Dr. Bressler and the safety data in this presentation, I will finally cover the assessment of the risk/benefit profile of verteporfin therapy in neovascular AMD.

At the time of the NDA submission, more than 1,000 patients were treated with more than 2,600 treatment courses. The clinical program included trials in clinical pharmacology, non-ocular studies, mainly in the areas of psoriasis and skin cancer, and also several ongoing and supportive studies.

One large ongoing study is the phase IIIb study, which is a larger placebo-controlled, masked trial in patients with pathologic myopia and mainly occult AMD lesions. Most of

the patients, however, were treated in the pivotal phase III studies and the phase I study where 544 patients were treated with approximately 2,000 verteporfin treatment courses.

The clinical program investigated several treatment parameters. These included drug doses between 3 and 20 milligrams per meter squared, light doses between 12.5 and 150 Joules per centimeter squared of the target lesion, and retreatment intervals between 1 week in the psoriasis studies and 3 months in the pivotal phase III studies. Most patients were treated with the recommended dosing regimen shown here in yellow. This was used in 402 patients who were treated with 1,790 treatment courses in the OCR002 study A and B, phase III.

The different clinical studies assessed several safety parameters. These included the visual acuity score, which was used as an efficacy parameter, but is also a very important safety variable. The results of vision assessments over time were summarized in the efficacy presentation. Patients were regularly assessed for the presence of any adverse events. This was done daily or weekly in the early pharmacokinetics and phase I studies. In the phase III studies, this was done 2 to 4 days after treatment and also

every 3 months before retreatment. Angiographic assessments were also conducted every 3 months to evaluate subretinal or intraretinal hemorrhage and the extent of fibrosis of the lesion. Finally, laboratory assessments were done daily and weekly in the phase I studies and later every 6 months in the pivotal phase III studies.

In the phase III safety summary that will follow, all adverse events are presented regardless of whether they were treatment related or not unless otherwise specified. At the data cutoff at the end of September 1998, some patients had already reached follow-up longer than 12 months and their adverse event data are included in this presentation.

Similar to efficacy, the safety results across the two phase III studies, OCR002 study A and study B, are highly consistent. Therefore, the safety data will be presented for both studies combined to gain more complete information from the larger sample size.

This slide gives an overview of safety data from the phase III studies. Overall there was a similar incidence of patients reporting any adverse event in the two treatment groups. Approximately 83 percent of verteporfin patients and 86 percent of placebo patients reported adverse events in the

studies.

2 percent of patients in each group died during the study. None of the deaths was considered associated with treatment.

Withdrawal from treatment due to adverse events was low, occurring in less than 3 percent in verteporfin patients and less than 1 percent in the placebo group.

16 percent of verteporfin patients and 17 percent of placebo patients reported other serious adverse events. Of these, less than 2 percent were considered associated with treatment in each study group.

Starting with the ocular safety results, any ocular adverse event that occurred at a numerically higher percentage in verteporfin patients compared to placebo is presented in this table and is also proposed to be included in the labeling. The most frequent ocular events were the ones summarized under the term "visual disturbance." These occurred at a 6 percent higher incidence in the verteporfin group. They included events such as abnormal vision, usually reported as blurry or hazy vision by the patients, vision decrease, and visual field defects usually reported as spots, halos, or scotomas.

For all the ocular events listed here, as you can see, the difference in the incidence between verteporfin and placebo is small, on the order of 2 percent for conjunctivitis or even less than 2 percent difference for the other events, dry eyes, eye itching, and subconjunctival hemorrhage.

Most visual disturbance events were transient. They usually occurred in the majority of patients within 7 days of treatment and they were mostly mild to moderate. Severe visual disturbance events combined together, shown here in yellow, occurred in less than 1 percent in each of the two study groups.

The phase III studies have prospectively defined four events as clinically significant ocular events. These were vitreous hemorrhage occurring at any time, severe vision decrease within 7 days of treatment, arteriolar or venular nonperfusion, and retinal capillary nonperfusion of an area equal or more than 1 MPS disc areas. The incidence of all of these events combined was low, as they occurred in 2.5 percent of verteporfin patients versus 1 percent of placebo patients. There were no cases reported with nonperfusion of normal choroidal or retinal vessels, confirming the safety margin of the chosen phase III dose regimen.

Severe decrease in vision as an adverse event was prospectively defined in the ocular studies as a decrease of at least 20 letters, or 4 lines, within 7 days of treatment. This slide displays the incidence of patients with this event in all placebo controlled studies in patients with CNV. These are the pivotal studies, OCR002, study A and B, which mainly included classic containing CNV lesions. They also include the incidence in the ongoing phase IIIb trial which mainly included patients with occult AMD and patients with pathologic myopia. As you can see, the incidence in AMD patients ranged from less than 1 percent in the pivotal phase III classic containing CNV lesions and up to an incidence of 4 percent in mainly occult lesions from study phase IIIb, OCR003. Overall, this occurred in 12 AMD patients out of 628 patients treated, or an incidence of approximately 2 percent.

A thorough investigation was conducted to evaluate the features of severe vision decrease events within 7 days of treatment. There was a small difference in the incidence of patients with different lesion components as shown in the previous slide, but there was no other predictable baseline or lesion characteristics.

In 7 out of the 12 cases, there was evidence of

increased subretinal hemorrhage, and in 4 out of the 12 cases, there was evidence of fluid or neurosensory detachment. There was no evidence in these patients of any normal choroidal or retinal vessel nonperfusion.

All patients except one reported the event following their first treatment course.

Finally, the event was transient in most patients as 10 out of the 12 cases showed more than 1 to 4 line improvement at the month 3 evaluation compared to vision score at the onset of the event. This included 1 patient who completely recovered to a vision score better than the pretreatment level.

In addition to the data on the definition and incidence of severe vision decrease in the clinical trials, the company is proposing the following labeling precautions to provide guidance to physicians on the management of such cases. "Patients who experience severe decrease of vision of 4 lines or more within 1 week of treatment should not be retreated, at least until their vision completely recovers to pretreatment levels and the potential benefits and risks of subsequent treatment are carefully considered by the treating physician."

Moving now from ocular to systemic safety, this slide shows a list of the incidence of patients reporting adverse events in each of the body systems. There were four body systems where the incidence was numerically higher in verteporfin highlighted here in yellow, and seven body systems where the incidence of adverse events was higher in the placebo group here shown in white. In the four body systems where the incidence was higher in verteporfin patients, the difference between the two groups was small, ranging between 2 to 4 percent difference. Most of the events reported under these body systems were considered to be not related to study treatment with the exception of some events reported under body as a whole body system, which will be summarized in the next slide.

In the body system body as a whole, the most frequent events were injection site adverse events which occurred in 10 percent more patients in the verteporfin group compared to placebo. The most frequent ones were injection site pain in 8.7 percent and injection site edema in 4.2 percent of verteporfin patients.

Photosensitivity reactions, usually in the form of mild or moderate sunburn due to exposure to direct sunlight

within 2 days of treatment, occurred in 3 percent of verteporfin patients.

A phenomenon of transient infusion related back pain was also reported in approximately 2 percent of verteporfin patients. None of the patients with back pain had any hematological or renal function abnormalities and pain completely resolved at the end of the infusion.

In the other body systems, the incidence of anemia and increased creatinine was 1 to 2 percent higher in verteporfin patients as shown here. As you can see, the difference is too small and most of these events were not treatment related and usually represented mild, transient laboratory abnormalities. This is not uncommon considering the mean age of the patient population of 75 years.

The most clinically relevant systemic adverse events, therefore, are the ones shown here, and they are shown with their severity grades. These are injection site events, photosensitivity reactions, and infusion related back pain. Most of these events were mild to moderate as shown in the slide. Severe injection site events were rare and only reported in approximately 1 percent of patients. Other severe events occurred with an incidence of less than 1 percent. In

general, even the severe events were still transient and self-limiting in these patients.

Since many of the injection site events were due to extravasation of the intravenous injection, appropriate guidance and precautions are proposed in the label for the treating physician. These are some standard precautions to avoid extravasation such as establishing and monitoring a free-flowing intravenous line using the largest arm vein possible and avoiding the small veins in the back of the hands where most of the severe injection site events occurred.

Verteporfin is a photosensitizer and as such, it will render patients photosensitive for a period of time. The evaluation of the photosensitivity period included assessment of time needed for complete elimination of the drug based on its short half-life of 5 to 6 hours and the fact that no measurable concentration was detectable in the blood beyond 48 hours in healthy volunteers.

Also by 48 hours, the skin photosensitivity returns to baseline levels based on rigorous photosensitivity testing in skin cancer patients.

In the more important ocular phase III trials, the photosensitivity precaution period was 2 days, and there

were 10 verteporfin related photosensitivity reactions out of 1,790 treatment courses. This is an incidence of .6 percent. 8 of these 10 events occurred during the 2-day protection period, indicating a noncompliance with the protocol's instructions. 2 patients reported mild reactions on day 3. Most importantly, there were no verteporfin related photosensitivity reactions reported beyond 3 days after treatment.

In order to avoid unnecessary burden on patients, we believe that the photosensitivity protection period should not be any longer than is necessary from the available data. We are currently proposing to advise the physicians that the photosensitivity protection period should be up to 3 days following treatment. During that period, patients should avoid exposure to direct sunlight or bright indoor light.

So, in summary, more than 1,000 patients were treated with verteporfin for injection in ocular and non-ocular studies. Of these, 402 patients eyes were treated with 1,790 treatment courses. The only clinically significant ocular events were transient visual disturbances, of which severe decrease in vision was reported in less than 1 percent of patients in the pivotal phase III studies.

Systemic events occurred at low incidence with small difference between treatment groups with the exception of injection site events. Events leading to withdrawal from treatment were less than 3 percent in verteporfin patients.

The safety results, therefore, support the conclusion that verteporfin therapy is safe and well-tolerated in patients with neovascular AMD.

From the efficacy and safety results, we can now assess the overall risk/benefit profile of verteporfin therapy in neovascular AMD patients. In the proposed patient population, with mean age of 75 years and a serious vision threatening disease, the risk of verteporfin therapy is small. There was a 6 percent higher incidence of transient visual disturbance events.

Acute, severe vision decrease within 7 days of treatment was low, occurring in 1 percent of patients in the pivotal phase III studies and up to a maximum of 4 percent in mainly occult CNV lesions.

There was a risk of systemic adverse events with a 10 percent higher incidence in the injection site events. This risk of injection site reactions could be mitigated by careful intravenous procedures.

Another clinically significant systemic event was the photosensitivity reactions. They occurred at an incidence of 3 percent of patients and less than 1 percent of administered courses. This risk could be minimized by patient education to maximize compliance with the photosensitivity protection period.

On the benefits side for the patient population proposed for approval, verteporfin therapy resulted in a statistically significant benefit in all primary and secondary efficacy endpoints. 28 percent more verteporfin patients responded to therapy as defined by proportion of patients who loss less than 15 letters. Significantly more verteporfin patients avoided loss of 3 or 6 lines of vision. On average, visual acuity was 2 lines better and contrast sensitivity was 2 segments better than placebo patients at the month 12 assessment. Lesion growth was confined in more verteporfin patients and more patients on verteporfin attained cessation of leakage. All these are important and clinically significant benefits in this patient population who do not have other adequate treatment options.

We therefore conclude that verteporfin therapy offers a favorable risk/benefit profile for the treatment of

patients with AMD who have predominantly classic subfoveal CNV lesions.

I would like now to turn the podium over to my colleague, Larry Mandt.

MR. MANDT: To conclude, we've demonstrated the following for the treatment of predominantly classic choroidal neovascularization secondary to AMD. Two adequate and well-controlled clinical trials have shown reproducible safety and efficacy of verteporfin therapy. In the phase III trials, the clinically relevant benefit, seen in the proposed indication population, reduced the risk of visual loss. The risk/benefit analysis strongly favors verteporfin. Verteporfin therapy represents a unique opportunity as a pharmacological treatment of an otherwise intractable disease.

To sum up, we believe that verteporfin therapy is a significant advancement for ophthalmology. The results seen to date are encouraging since a treatment benefit was seen in many AMD patients studied using the phase III regimen.

FDA has raised issues related to the retreatment regimen currently proposed for verteporfin therapy. We acknowledge that based on our results to date, verteporfin therapy is not for all AMD patients. There may or may not be

a more effective regimen, and we are currently evaluating the data generated to date to determine if potential enhancements to the therapy are necessary. However, we do believe that the proposed regimen has shown an important benefit in the treatment of predominantly classic CNV secondary to AMD.

To better understand the overall utility and long-term effects of retreatments, in some patients up to 4 years, QLT and CIBA Vision have already engaged in ongoing clinical evaluations of verteporfin. The existing phase III investigations have been extended and continue to study neovascular AMD in classic containing lesions. This open-label program adds 2 years of treatment and follows up the original study.

A study has been initiated to evaluate the effect of verteporfin in early neovascular AMD with mainly occult lesions. In addition, patients with AMD secondary to pathologic myopia are included in this trial. The trial is randomized, double-masked, placebo-controlled, and has enrolled 459 patients to date.

An open-label study in CNV due to ocular histoplasmosis syndrome has enrolled 26 patients.

And finally, a treatment IND protocol has been

initiated for the treatment of predominantly classic CNV enabling more patients with this type of AMD to benefit from the therapy.

The results from these studies will be evaluated and based on the results, QLT and CIBA Vision are committed to performing further research to refine the application of the existing therapy and explore potential new indications.

I would like to conclude by reminding the advisory panel of the proposed indication for verteporfin therapy. Visudyne therapy is indicated for the treatment of age-related macular degeneration in patients with predominantly classic subfoveal choroidal neovascularization.

With that, the company's formal presentations are complete. Thank you for your attention. We're now prepared to answer any questions you may have.

DR. FONG: Thank you.

I'd like to open the floor up to the committee and the members for any clarifying questions. I'd like to save more detailed questions until after the FDA presentation. Are there any clarifying questions at this time?

(No response.)

DR. FONG: I have one question. Neil, you

mentioned that 2-year data has been collected. Is there any possibility we can hear the 2-year data since a lot of this has to do with the long-term safety?

DR. BRESSLER: You can't hear any of the 2-year data yet because we're still in the process of compiling it. The patients completed their 2-year follow-up just at the end of September, and as you can imagine, we don't necessarily have all the photographs in yet to analyze them and we don't have all the data checked and double-checked. Until we've run that analysis, we don't have it. So, at this time, we just don't have any of the 2-year data.

DR. FONG: Jack?

DR. CIOFFI: Neil, you presented the combined A and B study for the secondary endpoints, and although the primary endpoints showed consistency between the two studies, I'd be curious to see the secondary endpoints broken down into A and B to see if they equally show replication.

DR. BRESSLER: They did and I didn't bring my notebook up, thinking about clarification slides. But I can put those up now. If you want to, we could do that right after the break where we have it by A and B. So, why don't I pull those up after the break as your first question so I

don't have to waste time to do that, but I will do that to show you what we have with study A and B. I don't know if you're going to show those, Dr. Chambers.

DR. CHAMBERS: I'm not, although I do agree that they are consistent with what you've already seen.

DR. BRESSLER: Yes. So, I'll pull it up so that you can see it at the beginning of the next session, if that's okay.

DR. FONG: Johanna?

DR. SEDDON: Yes. I had one question, Neil. Apparently in the placebo group, 42 percent of those individuals had blood and 33 percent of the Visudyne group had presence of blood. Is that correct? There were more lesions with blood in the placebo group compared with the Visudyne group.

DR. BRESSLER: Yes.

DR. SEDDON: What were the differences in the size of the lesions between the two intervention groups?

DR. BRESSLER: The sizes were balanced throughout. When we did a distribution of less than 3, 3 to 6, 6 to 9, and then there was 1 percent that were greater than 9 at baseline, the numbers are almost right on top of each

other.

DR. SEDDON: In your slide 68, it was interesting that only one of the size subcategories had a statistically significant difference. So, I was wondering were the results presented, all controlled for size of the lesion.

DR. BRESSLER: Why don't we pull up slide 68?

Okay. So, this is looking at the subgroup analysis by the lesion size at baseline, and this is for the entire study group, just to get everyone reoriented again because of all the slides. What we're looking for here is whether there's any harm to the treatment, first of all, and there's not. It's always beneficial for verteporfin regardless.

Then we looked to see is there any obvious trend to suggest that there's a difference in the interaction between these, and we couldn't see a statistically significant trend across them.

Although we put the p values on here, that is not relevant to answering the question, does size appear to affect the treatment benefit. So, it's beneficial for all of them, and when we look at smaller and smaller subgroups of numbers, we may not get a statistically significant benefit.

DR. SEDDON: But the final results were adjusted for size of the lesion.

DR. BRESSLER: Yes. When we did a multivariable regression analysis, size was put in as an important parameter to that, and it did not affect the outcome that was seen.

DR. SEDDON: All right. Thank you.

DR. FONG: If there are no further questions, I'd like to take a 15-minute break at this time. I want to remind the committee members not to talk about the issues being discussed today. We'll reconvene at 10:45.

(Recess.)

DR. FONG: The next thing on the agenda is the FDA presentation. Wiley Chambers, Deputy Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products will be making the presentation for the FDA.

DR. CHAMBERS: Thank you, and good morning. My name is Wiley Chambers. I'm the Deputy Director for the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products, and for this particular application, I also have performed the primary medical officer review.

The proposed indication, as you've seen now multiple times, is for the treatment of age-related macular

degeneration in patients with predominantly classic subfoveal choroidal neovascularization. The data that I will be presenting is the same that has been previously presented by the sponsor, although I have performed a complete reanalysis of the information, and I may choose to emphasize a few different aspects than you've heard earlier this morning.

The sponsor has been advised of the issues that I raised as I reviewed the data, but they have not seen the briefing document that was sent to the advisory committee members and they have not seen a copy of my review.

Since you've already heard the details of the individual protocols, I will not repeat the individual details of the protocols.

The dose-ranging study that was performed looked at a number of different regimens to try and determine what was the best both time and dose to administer the drug product and the subsequent laser light. As you can imagine, there is an endless possibility of different drug dose amounts and durations of time and energy that could be applied. So, this was an attempt to try and pick out a few different ones to try and learn what would be the best to go and decide.

The agency is in agreement with the sponsor that

of the different regimens that were tested, the one that they selected was the one that performed the best. In this case, it is regimen number 4.

At the 1-week time point, green is identified here as complete closure. On later graphs, you'll see some red, and red is a progression. So, that's the worst. But the ideal would be if there was green all the way through.

At week 4, you already start seeing some leakage. Again, while regimen 4 is the best of the individual regimens that were tried, it is still showing some leakage, as demonstrated in the yellow and white, and all the way to a progression in approximately 14 percent of the people by week 4.

This continues at week 12. Again, you continue to see at week 12 regimen 4 is the best of the regimens. However, there is significant leakage that is occurring in a sizable portion of the patients.

This leads to the question and led to the issue of what should be done, or is there a particular concern that there is continued leakage before the next treatment?

For each of the individual slides that I go through now, I will show what is either study 1, or study A,

listed on top and study 2, or study B, listed below. So, each of my slides going through will show each of the individual studies separately.

The cumulative number of treatments obviously increased as we went through each 3-month interval. You see the majority of people needing an additional therapy at each 3-month time point. Some patients were able to skip one 3-month period of time as you went along, but the vast majority of people need therapy every 3 months. And the two studies show very similar results.

You've heard a little bit about we've raised the issue there were some discrepancies between the reading center and the individual investigators. The treating centers did not always report leakage, while the reading center virtually always identified additional leakage in their evaluation. The agency has reviewed a portion of the slides that were obtained and the agency is in agreement with the reading center on their evaluation. Whether this is a significant issue when the product would be used in clinical practice where individual physicians would not have the benefit necessarily of a trained reading center, I leave open as a question to the committee.

Clearly you can see, if you take a look at the reading center lines, you can barely see because -- this is the percentage of patients with no leakage, and you see a very small percentage of people with no leakage as reported by the reading center. Even the treating centers never report more than 30 percent of the people not having leakage.

There is a slight tendency based on the treating center information that there is less leakage as you go along on subsequent therapies. It's not as dramatic if you look at the reading center data.

The agency suggested that a minimum of a 2-year follow-up be performed for any of the macular degeneration studies, however, was willing to accept results at a 1-year time point for submission of a new drug application with the feeling that if a visual acuity benefit was demonstrated at 1 year, that that would be sufficient benefit for patients and that therapy might be deemed approvable at that particular point in time.

Recognizing that the disease will continue for the lifetime of the individual patients and that additional data would be needed, we requested that anyone pursuing these indications pursue trials that went for at least 2 years and

that that information from the 2-year follow-up and subsequent, if performed, would be included in the labeling of the product at the time that that information became available.

Visual acuity clearly declines in both groups. Again, this is study A and study B you've heard about so far. These are mean visual acuities going down. These are standard errors that are displayed here. You see, starting essentially the same in each case, and a clear separation going on between the mean visual acuities. The difference here, as has been pointed out before, is approximately 10 letters in each case.

The agency generally has not accepted this as a clinically significant difference in looking at mean differences. However, as has been described before and as I'll show later on, doubling the visual angle, or 15 letters, and percentage of people with 15 letters we do believe is clinically significant. Had this been the only factor along, we probably would not have viewed this as being a clinically significant difference.

The results, as you can see, we agree are also consistent between the two different studies, and we have considered them robust in that both the per-protocol analysis

and the intent-to-treat analysis with the last observation carried forward show consistent results.

As has been described before, an alternate method of performing an analysis -- and this analysis was preselected prior to the study commencing, was the percentage of people with a 15-letter loss. As you can see from study A and study B, the percentage of people with a 15-letter loss is higher in the placebo group in each case, starting obviously initially at baseline but separating and becoming statistically significant by month 12 in both cases. This 15-letter loss we believe is clinically significant. What's displayed here is the last observation carried forward. The intent-to-treat analysis looks the same.

Although not a primary analysis, I have also displayed here a 30-letter loss. The 30-letter loss has a hint of leveling out, although it's difficult to determine whether this will persist and whether it is due to a bottoming out effect where patients only have a certain number of letters to ultimately lose. So, it's impossible for some people to lose obviously more letters than they had to start with. So, it would be expected to be some kind of leveling out effect along here. But there is a clear separation even

for a 30-letter loss in both studies.

I have not shown the contrast sensitivity results and that is because I do not believe that the differences seen in the groups is clinically significant. There are numerical differences as was shown by Dr. Bressler, but I do not believe that they are clinically significant.

There has been a lot of discussion and I expect further discussion by the committee on the different subgroups and trying to identify where there is a clear effect, who would best be benefitted by a potential therapy. Clearly the patients with a 50 percent classic lesion or more and no occult lesions are more likely to benefit from the verteporfin treatment.

These two tables show in decreasing frequency for the Visudyne treatment, which are the blue letters going down -- they are ordered in order of decreasing efficacy or 15-letter loss, and the same thing in this trial. You'll notice a couple different things as you look at the different groups. The placebo group does not always behave the same and does not follow the same similar pattern. The same thing along here. It averages out along here, but the subgroups don't necessarily correlate with the Visudyne treatment. In other

words, there are some subgroups where patients do better regardless of whether they are placebo or on Visudyne.

Clearly you see the difference that's here with an occult and a 50 percent classic. You see the same thing along here with the no occult and the difference here in 50 percent classic.

Patients with a poor vision at baseline, smaller lesions, or younger ages are likely to have better outcomes regardless of which group they were in.

Women also were shown to generally do better whether they were in the placebo group or in the Visudyne group.

One of the things not mentioned to date was a quality of life assessment that was done on a subset of the patients from study A and study B. This was a subset of the people from each of the two different studies, and an attempt to use a quality of life measurement was performed. The two marks identified in yellow here happen to come out nominally statistically significant if viewed alone, and they are in the reverse direction. The placebo does better than the Visudyne group. However, if you were to correct for the multiple comparisons -- and this is clearly many multiple comparisons -

- these things are not statistically significant. So, the bottom line from the quality of life measurement that was performed was that there was no difference between the groups to the extent that this measure had any power to detect any difference, but it was obviously hoped that a difference could be shown.

Going on to some of the safety information, most ophthalmic drug products don't tend to have large numbers of deaths in their clinical trials, with the exception of some of the longer-term glaucoma trials where we have patients that are 80's and 90's when they go and enroll. This study, as has been described before, had a mean age of 75. There is no clear pattern that has been identified as for the reason for any of the particular deaths other than they are the typical things that happen to patients that are between 60 and 100 years of age. If anybody from the advisory committee sees some pattern to it, I would be interested in hearing it, but we were unable to find any particular pattern.

Serious events you've heard a little bit about. There are clearly patients that have acute, significant losses of vision that are early on. The percentage is relatively low. A significant portion of these patients do have some

vision return after the first week. The etiology of some of these severe losses is unknown. There was no clear finding from the measures that we took of why the severe vision loss occurred, but we do believe it's important for individuals potentially taking the therapy to be aware of the potential risk of having a severe visual loss in close proximity to the treatment time.

There were also some severe losses in the placebo group. That does not necessarily mean it couldn't be from the laser therapy, although this laser power is relatively well known and well studied.

I've selected out the individual ocular events that occurred more frequently in the Visudyne group than it did in the placebo group. So, this is not a complete list of all adverse events, but these are just the events that were seen more commonly in the Visudyne group than in the placebo. When I say more commonly, I mean literally just numerically higher. They are not all statistically significant. In some cases the percentages are relatively small because the total numbers are relatively small. But it suggests the same types of events that you've heard a little bit before, conjunctivitis, some vision abnormalities, itching,

nonspecific events, that were more frequently occurring in the Visudyne treatment.

From the systemic perspective, there were nonocular events. You obviously heard about the injection site events being more frequent, nausea. Back pain has been addressed because of the potential implications that back pain could be, although no specific identifying event or cause has been established with the back pain.

The agency has raised the issue with the anemia that's here because the laboratory also found a slight hint toward anemia. We're not talking about an aplastic anemia type of event. These are relatively mild changes that have been observed.

The same thing with the creatinine increases. They are relatively mild changes but there are differences between the placebo group and the Visudyne group. One of the questions obviously for the committee is, does anybody believe that this is a marker for something else that's going on?

And you see the other injection site reactions.

To express a little bit more clearly what I'm talking about as far as the hematological events -- and again, you'll see these are relatively small numbers of patients.

We're only talking about 6, 5; in white blood cell count, 2 and 6, and yet there is no difference here for the hematocrit. I'm just suggesting it as a -- because there is a difference between the different groups, don't have a particular cause, and don't know that this necessarily could not have happened by chance.

Creatinine also is identified here. Again, we're considering relatively small percentages, but the comparison between half a percent and 1.3 percent and half a percent and 2.7 percent for the creatinine.

There was also a difference in AST and ALT, the liver function tests, but that's primarily because these are 0's in each case for the placebo. So, even though only a couple events looked different, but it's questionable whether you would make anything of this at all.

In summary, based on the information and based on the briefing package, we've identified a number of issues which the agency would like the committee to discuss. They are just stated as particular findings going through, and the agency would be interested in any comments that the committee members have on any of these issues.

Dr. Fong, do you want to address questions before

we go into the individual issues, or do you want me to just run through what these issues are and then you can address questions and then come back to address the issues?

DR. FONG: That's a good idea.

DR. CHAMBERS: Okay, just so that everybody sees what the issues are.

All patients continue to lose best-corrected visual acuity.

The lesions demonstrated leakage within 3 months of treatment. Obviously the goal would have been to have people go longer periods of time without leakage.

Repeat treatments have not been studied at intervals less than 3 months. The studies were all designed to essentially look at treatments every 3 months with the exception of some very early work, but it has not been extensively looked at for any kind of treatments other than every 3 months.

Repeat treatments have only been studied out to 24 months, and only the 12-month data has been submitted to the agency. As you've heard, the 24-month information has recently been completed and has not been audited and submitted to the agency as of yet, though obviously there will be an

expectation and a commitment from the company to submit that as part of any action by the agency.

Bilateral treatments have not been adequately studied. It doesn't mean there haven't been some bilateral treatments, but for the purposes of keeping the data relatively clean and not initially exposing people to an unknown therapy until we had more information, the initial studies did not include bilateral therapy. Clearly it would be in the patients' best interest to have only one injection and receive light treatment in both eyes, if they needed it in both eyes, and not have to go through two injections. The exact best way to do that is being worked on but has not yet been established, but obviously will come up if this therapy were to be available to the general public.

There are some discrepancies that existed between the reading center and the treatment centers, the reading center being more sensitive. This is not an unusual finding. It is true in most cases where we have reading centers.

Photosensitivity. There were 48-hour precautions. As demonstrated in the adverse events that were displayed, there were clearly patients that, in spite of this warning, had photosensitivity reactions, including at least

one that was severe. The drug, in theory, should be gone within 48 hours, but there is a question about any effects linger on beyond that and what is the best way to have patients understand that they need to stay out of the sun while they have the drug on board. A number of photodynamic therapies, not in the ocular area, have had extensive warnings for up to 6 weeks as far as warning people to stay out of the sun. Those are generally with products that have longer half-lives than this product does. But trying to find a way in which patients can be adequately informed to avoid this problem remains a concern.

As I mentioned, there are signals about anemia and creatinine increases. They are not clear indications that there was a problem with the product. They were just early signals, and I would be interested in any comments that the committee has on how strong a signal you believe this is.

Then we'll get into the questions afterwards. And I'm open to any questions.

DR. FONG: Jackie?

MS. GOLDBERG: It's just a point of clarification. Could you go back to the quality of life slide and repeat what you had said previously and if you know

anything about the particular measures or the value of the measures? Thanks.

DR. CHAMBERS: I'm sorry.

MS. GOLDBERG: Could you just repeat what you had said previously about it and elaborate it at all, if you can?

DR. CHAMBERS: A quality of life questionnaire was given to a subset of patients in both A and B. This is information collected, although it's a relatively small subset. There are 56 in the Visudyne group and 33 in the placebo.

This quality of life instrument has been reported to be validated by the National Eye Institute. It has not, in the past, been used for any drug trials as far as ultimately establishing efficacy. It has been used in other trials, but has never been shown to establish efficacy, as far as the agency is concerned, to date.

The findings that were demonstrated were in the reverse direction. The placebo did better than the Visudyne, but if you take into account the multiple comparisons that were done, none of the findings are statistically significant.

Other points of clarification?

DR. FONG: Any more clarification points for the

FDA? Jim?

DR. KILPATRICK: Wiley, this is a general question. The sponsor has asked for approval to market this Visudyne for a special class of patient, predominantly classical CNV. The phase III trials were approved by the FDA and the sponsors beforehand. Why were the subjects not restricted to that particular type of patient, and why did more general AMD patients get included?

DR. CHAMBERS: The criteria that were identified are primarily identified by fluorescein angiograms. The call on exactly what type of classification people have is sometimes a judgment call by individuals, and the approximately 9 or 10 percent of patients that were enrolled that did not have all the features that were expected -- it's not that they didn't have some of the features; they didn't have all the features that were expected -- can be considered a judgment call between the reading center and the treating centers. And I don't have a disagreement that that type of thing would happen.

DR. FONG: At this point I'd like to open up the floor to discussion on all the issues and questions to both the sponsor and the FDA.

Well, Neil, I have a question for you. To follow up with Dr. Kilpatrick's question, I think that's an excellent question. If we're talking about approval of this drug for a subclass, that is, eyes with classic neovascularization, why wasn't that stratification included in the design phase of the study?

DR. BRESSLER: We had very limited information from the phase I and II studies, which again were limited based on just some animal studies. In the phase I and II studies, we noted that there appeared to be quite a prominent effect of stopping leakage on classic neovascularization, and the effect was not quite so apparent on occult. This was a subjective evaluation and some data behind that.

We thought then that the therapy might work better if we require that a case have classic neovascularization. So, that was one thought.

In addition, we suspect that cases that have classic neovascularization are more likely to deteriorate within a year or 2 time period, and cases that don't have any classic neovascularization we know sometimes can remain with very stable vision for years. So, until we had more experience using this just safely, we were reluctant to begin

to treat people that didn't have at least some classic neovascularization. Therefore, the design was, let's take the universe of AMD patients who at least present with some classic neovascularization.

Now, on top of that, we thought it's possible that this may have an effect on cases that have lots of classic neovascularization because if you're going to admit anyone who has some classic neovascularization, that could be 1 percent or 99 percent. So, we decided we better do a subgroup analysis that tells us are the results consistent whether they had just a little classic or a lot of classic. And in fact, we found the results were not consistent. They appeared to benefit cases that had a majority of classic neovascularization.

So, to summarize we thought that the cases with any classic neovascularization had a greater likelihood of deteriorating, and until we had more experience with the drug, we only wanted to start with that. And in addition, we needed to look at whether that classic neovascularization from just a handful of cases in the phase I and II really could potentially have a big impact on the study, and it appeared from the analyses that it did. So, we think the best thing so

far would be to recommend this to that subgroup with predominantly classic.

I might add that once we had some experience treating -- we knew it was 600 enrolled but only 400 got drug -- and once they had been treated once or twice or three times, we then expanded a second trial, this phase IIIb trial to look at cases that were predominantly occult neovascularization so that if we thought it was a little safer now to try that, we could find out, which we will 6 months from now, if that group benefits as well.

DR. FONG: Thank you, Neil. I guess my concern is that we're seeking approval for classic neovascularization, and yet the data for approval is from a subgroup analysis. I think you've already pointed out all the difficulties with interpreting information from subgroups.

Are there additional studies that are going to be looking at stratifying classic neovascularization, with lesion size, blood, and all those other potential confounders as part of the study for this drug?

DR. BRESSLER: Well, let me go to the first part. I agree. I love subgroups and I hate subgroups. I love them because I think you want to learn as much as you can from the

data that you have, but I think you want to be very cautious about ever making a recommendation on that. That's the part that I hate, if somebody decides to do something usually based on a subgroup.

However, I think this is a good example in clinical trials as to the exception where when we prospectively thought this group might do better and they do have a very, very strong benefit, and the group that did not have predominantly classic lesions had no difference that we could see for our primary endpoint, I think it's good to start with just this smaller group.

Now, that group that did not have predominantly classic lesions did benefit angiographically and with respect to contrast sensitivity, but that gives us less faith that we should go out and recommend that as a treatment so far.

So, I do feel very comfortable in this particular trial that went on to make a recommendation based on a study when it is really the exception.

Now, are we going to do additional studies to see if this is just a fluke of that subgroup? I don't think we have to do an additional trial where we enroll just predominantly classic compared to placebo to see if this was

some fluke because the numbers were large enough, consistent enough and, in every which way we looked at it, made sense, that I don't think that that's warranted.

I do think that this is the first step. You found that this worked. You had a theory it might work. You had some preliminary information saying it may have worked, and now in a good rigorous trial, it has some benefit. And, yes, I think you want to find out what are all the different situations this may or may not work. I think we want to mind the data first that's here, go through the angiograms in detail, go through progressions in detail, and see if we can come up with better regimens.

DR. CIOFFI: Don?

DR. FONG: Jack?

DR. CIOFFI: My question is related to this issue and actually it's probably my principal concern today. To paraphrase Mr. Mandt, he said, this isn't a treatment for all AMD patients, in one of his concluding remarks. I'm wondering if, in fact, the average ophthalmologist is going to be able to differentiate who this is a treatment for. To illustrate that point, 9 percent of the patients were thought to have classic neovascularization by the investigators, but you said,

no, they didn't have any, and a very, very large percent were found to have leakage by you at the reading center but not by the investigators. That worries me that the average ophthalmologist isn't going to be able to tell who needs to be treated and then who needs to be retreated later on without the assistance of a reading center which won't exist, I don't presume, down the road.

DR. BRESSLER: I think your concerns are good, and I want to take them as two separate issues because one is just identifying the cases that may benefit, and the second is something that Dr. Chambers brought out, and that is, well, what about deciding to retreat based on leakage? So, let's take identifying the cases that may benefit.

A 9 percent difference for identifying classic neovascularization, given the continuum of what makes an ophthalmologist say something is classic or occult based on the brightness and the uniformity of that fluorescence, to me I think is just an acceptable real world thing of experts, that if you have some retinal experts used to looking at angiograms, that they will probably differ on that I think 10 percent of the time as a good thing. So, I don't think the average ophthalmologist necessarily yet is comfortable in

reading fluorescein angiograms and making this differentiation for at least the first step of who should be treated and who shouldn't be treated.

So, I think it's important, now that we have a reason to train and educate people to recognize this, to go out and say, here's the therapy, here's some real strong information about who you want to treat, and now you've got to be able to recognize these differences. That's got to be through continuing medical education courses. That's got to be through monographs from the Academy. That's got to be from us talking to each other individually, looking at cases at the light box or on a screen, and learning that.

And I think it can be learned. There's nothing smarter about someone who reads these all the time versus someone who doesn't except what they've concentrated on. So, I think it can be done and it's got to be done, and I don't think it's necessarily something everyone has right now as the average ophthalmologist because there wasn't a need to.

Now, let's go to the leakage question at follow-up. What are we going to do about that? If we could summarize what was shown at month 12, it was about 24 percent of the time the ophthalmologist saw no leakage when the

reading center saw leakage. So, what do we do about that?

Well, I know that when we have the ophthalmologist make the decision for predominantly classic lesions, I know the therapy works. So, whether they call up a reading center or not because they didn't have the opportunity to get our opinion, we wanted it to represent what would happen in the real work if this worked. We know that it is going to work and that it works substantially. I think that 28 percent difference for the predominantly classic is a real benefit.

Now we have to figure out if they followed what the reading center interpreted, was that a better or worse thing? Maybe it is better to keep treating that. Maybe the reading center has to set their rheostat. Maybe they're too sensitive at picking up the tiniest little bit of leak, and when it's real tiny and the ophthalmologist who's looking at the patient sees no subretinal fluid in the eye, sees that the vision is the same and is biased subconsciously to say that tiny bit of leakage -- it was questionable. I say none. Maybe that's the better way.

So, this was our first attempt at a protocol, and it worked not relying on the reading center. If we had these

results and they had sent the angiograms in relying on the reading center, then we would have been concerned that when we let this out in the general public, maybe the ophthalmologist has to send it to a reading center if they have to retreat or not. So, at least, I'm not concerned about that, that when somebody is trained, following this design, at least they'll benefit.

The question is will they benefit more if they went by the leakage from the reading center or would they benefit less. Maybe if we did retreat it at every single time, maybe that would be more harmful. So, this needs to be looked at to figure it out.

DR. CIOFFI: So, am I to understand then that you did not give feedback back to the treating center about leakage?

DR. BRESSLER: That's absolutely correct, and that was very purposely chosen because of this potential problem. What if it works? If it works, you don't know if you have to send it to a reading center. Now, that would make for a big reading center, so that could make a nice little industry there, but we weren't looking for that.

(Laughter.)

DR. BRESSLER: And it wasn't practical. We were looking to see if this works in the hand of an ophthalmologist trained with these rules, great. Now, we have a reading center to ensure objectivity, consistency across centers and to explore for new things. And here's a new thing. Should we adjust to this leakage or not? And we have to analyze this and maybe test it in some other ways as well.

DR. FONG: Johanna?

DR. SEDDON: I had exactly the same question actually, and thank you for answering most of it.

DR. BRESSLER: It's important I agree.

DR. SEDDON: But I think maybe just to expand upon this, it is a predominantly classic subfoveal choroidal neovascular membrane that you're suggesting the indication be. So, that requires a very well informed, well trained ophthalmologist to distinguish predominantly classic so they must distinguish classic from occult and what predominantly classic means and also subfoveal from juxtafoveal and extrafoveal choroidal neovascular membranes. So, I think that's particularly relevant given the facts that were just presented regarding the discrepancies between the ophthalmologist and the reading center.

So, I think you're right. Definitely education is needed and training. But what are the implications, in terms of the anticipation that this will be used by general ophthalmologists, that this will then be taken as an avenue for treating all the other types of choroidal neovascular membranes? That was the concern, I think, when this is being discussed in the media right now as the cure for macular degeneration and many patients and perhaps physicians will think of this as an indication for all choroidal neovascular membranes. So, I think we perhaps need to discuss that somewhat.

It might have an implication for how this is labeled and that is one of the items for discussion here on adequate labeling of this particular drug and how it will be used.

DR. BRESSLER: So, I've had the same concerns, and it gets back to again part of the education will be to emphasize to whoever thinks they're going to do this treatment -- and that's got to be people who are comfortable in analyzing these angiograms and treating the macula with the laser light. It comes down to educating those people to understand the clinical trial results because we have to be

very strong in explaining to them if you have no benefit so far for a lesion that's not predominantly classic, why you shouldn't necessarily give in to a patient who's sitting there, like some of our patients discussed today, who are very bothered by this loss of vision and say, oh, I can do this. I think we have to train the ophthalmologists to not only understand when to enter a case, but what the limits are of the therapy.

I believe one way of doing that is to label it for predominantly classic, first of all, so people recognize this has gone through some very careful peer review not only here, but when we published this and when we discuss it with our peers.

If people think that they can use it on just any case, they will learn over time that they have patients who are not doing well, that they don't have many patients who are stabilizing at all, and maybe this will shake out. Or maybe we'll find better ways of treating it so that we can treat those other cases. So, I share the same concerns, but that wouldn't make me -- and I'm sure you feel the same way -- want to withhold this treatment from someone who could identify a predominantly classic lesion and go ahead and apply it to some

benefit compared to no treatment.

DR. SEDDON: No. I totally agree. I just think we need to be cautious in how we discuss the indications and limitations of the treatment.

DR. BRESSLER: I agree.

DR. FONG: Leon?

DR. HERNDON: I have some concerns about the frequency of retreatments. This is a modality that you are giving every 3 months. Showing the 2-year data will be interesting to look at.

Is there a point when you stop, when you don't give more treatment based on the literature that you know?

DR. BRESSLER: There isn't a point that we stop yet for the trial, but remember, when designing the trial, we didn't know what the results were going to be so far. So, we chose a protocol that we said we hope it stops leaking. We hope it stops growing. We hope the vision stabilizes, and we don't know if that was going to happen at 3 months, 9 months, 18 months, or 24 months.

So, first of all, we don't necessarily have to treat everybody every 3 months through 24 months. I already showed you that we saw at least through 12 months that the

number of cases that are getting treated is decreasing. So, that implies to me that this won't go on indefinitely.

In addition, qualitatively if you look at the angiograms, you notice that there are cases -- and I don't know if they've gotten treatment or placebo, but I know from looking at some of my cases that I'm no longer treating that this does stop leaking and you do stop treating.

We should and will come up with guidelines I think as ophthalmologists as to when you should consider stopping treating. For example, someone who stops leaking and stops growing, you should stop treating. So, that's straightforward.

Someone who perhaps drops to a very low level of vision, started for example at 20/100 and despite treatment, dropped to 20/800, maybe I would believe it's no longer going to be of benefit to give them the treatment. And I think this will come out in guidelines to people.

Someone who I've treated and it grew from, let's say, 3 disc areas to 12 or 16 disc areas, that's terrible. I wish it wouldn't happen, but obviously nothing works in everyone all the time. So, we may come up with some guidelines to say, you know, once it's grown beyond this point

and you're not getting any vision benefit, you probably shouldn't treat.

So, I agree we need it, but I think it's going to depend on further data we get from the 24-month follow-up. For now, all you can tell a patient is this is beneficial to you for the first year if you meet these criteria. We don't know yet how long treatment would go on, but I'm comfortable saying it's not likely to go on indefinitely.

DR. FONG: Well, I'd like to echo Leon's concerns. I think that the benefit that has been reported is not huge, and it's temporary. I think Dr. Chambers' presented to us that the mean visual acuity at 1 year did not reach the 15-letter difference that was a priori decided as a clinically significant difference. So, the benefit is small, appears to be temporary.

I'm concerned that there is not enough long-term data on the safety of this drug. Leon has pointed out and you've pointed out that patients need to be retreated every 3 months, and it doesn't seem like we know what the side effects are, what the adverse events are going to be with repeated treatments.

I haven't seen -- maybe you have this data

looking at the retinal pigment epithelial changes with repeated treatment. If 2-year data is available, I think that it's real important to see that to look at the overall safety of the drug because how would the committee feel, for example, if in 2 years the benefit completely reversed itself, that patients who are treated now are worse off? How would patients feel about that? Without that information, I think it's really difficult to know what the safety aspects are.

I think looking at retinal pigment epithelial changes are important, maybe some electrooculography to look at the impact on the retinal pigment epithelial cells. I would just hate to repeat the approval process for a drug like ecainide or flecainide where early on you see a very convincing beneficial effect, but long term patients are worse off.

DR. BRESSLER: Well, let me go through these points. I'll find it helpful if we could put slide 78. Slide 78 is the predominantly classic group. This is the group for which the approval is being suggested.

Let's go back one to 77. Now, this is the average visual acuity change. So, this is where on average treated patients continue to lose vision throughout the 12

months. This is where there's a 6-letter difference here.

I don't have the right one. I want the one in my presentation. That's for the entire group. My presentation slide 78. I'm sorry.

But we're going to look now just at the predominantly classic subgroup and we're going to look at the difference in the mean visual acuities over time. This is where we have a 10-letter difference which is about 2 lines. I wouldn't equate having an average 2-line difference as the same as our saying 3 lines is a clinically relevant difference. The 3 lines being a clinically relevant difference in my mind is for someone who -- an individual starts, for example, at 20/100 and drops to 20/200. That's a clinically relevant effect. And someone who starts at 20/40 and drops to 20/80, that for that individual is a clinically relevant effect.

So, we chose not an endpoint where this was going to be 3 lines, where the average was going to be 3 lines. We chose what percent of people would have that outcome of what we thought was clinically relevant, 3 lines or worse. That's where we get this two-thirds/one-third difference.

So, if we go to the next slide, to me this

summarizes all of the data in the best way. It's true that we have people who received verteporfin therapy who lost vision shown in the green bars here, and the clinically relevant ones that lost vision, when it's 3 lines or more, that's these 21, 33, 34 percent. The clinically relevant ones that lost vision with placebo was -- here we have about 53, 60 percent. This is to me a big difference; that if your chance of going down here is this amount versus this amount, to me that's a big difference. And not everyone lost vision over time.

So, not everyone lost vision over the 12-month time period. You can see that these people here did not lose vision. They stabilized. Maybe these improved. This 5 percent had a big improvement. But at least we have not only that 5 percent, but these additional ones that stabilized.

So, I think you don't have to have an average 3-line difference. To me that is different than saying a responder who has a 3-line change, that to me is clinically relevant, and so I look at this and say, how many percent people had those changes going on? And that's the difference between these three green bars and these three purple bars. So, I do think this is very clinically relevant.

To your second point --

DR. FONG: Neil, before we get off this issue, I mentioned to you my concerns about a subgroup analysis early on. How would you present the same data using the whole group rather than just the subgroup on classic?

DR. BRESSLER: That was that other slide. So, we can look at that, although again we're not recommending that the entire group of lesions that met these criteria at first be entered into the study. So, let's look at slide 78 of the backup slides I think that is. That's the one that we had up there first.

For that, it's the same answer, but the differences are smaller. The differences are smaller because there does not appear to be a visual acuity difference between the placebo and the treated patients when we have the entire group thrown in here. So, again not every treated patient for the entire group loses vision.

You can see the green bars here have a higher percentage than the purple bars here. The differences aren't as great, and we're not recommending that this entire population get treated. But even so, here we have 30, 48, 53 percent of the purple bars having a clinically relevant decrease, and here we have 24, 34, 38 percent in the treated

group. So, for the entire population, that was relevant and it did work.

It wasn't as great a difference to make me want to recommend to these patients yet, especially when I look at what's behind this information, and that is, that for the predominantly classic group, they're doing much better.

Now, I did want to mention the appropriate concerns about what's going to happen if this reverses. We don't know, and that's why it's critical that we collect 2-year data, which we did, and it's critical that we analyze that so that if it remains the same, we have the same comfort level. If it improves, we're even happier, and if it reverses, then we have to weigh, well, is it worth giving this person a year's worth of vision increased chance versus having worsening vision later on? That would be a judgment call that, in general, most people might be reluctant to do depending on how much that reversal is.

But if we go back to the main presentation slide 78 of this, again let's go back to the group for which we're recommending this. The amount of damage you'd have to have to reverse these outcomes by 2 years will be a lot, and there's nothing that we've seen in the first 12 months happening to

suggest that something is going to happen later on. That doesn't mean we shouldn't look because plenty of times things happen that we didn't expect, so we have to look. I don't see it yet. I'm comfortable telling a patient I don't know the long-term outcome yet. I know that in the first year this is, on average, going to give you a better outcome than without. So, that's why I don't think that that will be a big problem unless we see something happen later on.

In terms of atrophy, we graded the size of the damaged area at every follow-up in the reading center, and we did a grading just of the neovascular lesion, and then we added to that the lesion plus any atrophy surrounding it. We didn't look at atrophy within the lesion because the pigment epithelium is already disturbed within the lesion itself. But we said, are we causing additional atrophy around the outside of this? And at each follow-up visit, the size of the lesion plus the atrophy, whatever harm we were doing with the therapy, was always less than the size of the lesion plus any surrounding atrophy in the cases left alone. So, if it does cause some damage to the pigment epithelium, at least within the first year it's not more damage than if left alone, and at least within the first year, it's not associated with more

vision damage than if left alone.

So, these are concerns, and if we can come up with something that will be even less harmful to the pigment epithelium, I think that's great as well. We've shared all these concerns as well, Don. I agree.

DR. SEDDON: Neil, when will that 2-year data be available? You said they have been collected and they're being managed and analyzed now. Is that correct?

DR. BRESSLER: I'll give you my best guess. My best guess is that if it took until January working only on that data one year ago, when we had the 1-year follow-up come in, and now we've got two trials going on and people working as hard as they can to get all this regulatory information in and collect that data and collect the 2-year data, it may take just within a few months after that.

Larry?

MR. MANDT: Go ahead, please.

DR. BRESSLER: Okay. So, my best is it's going to take within a few months after January to look at that to have that available.

DR. FONG: Dr. Kilpatrick?

DR. KILPATRICK: Dr. Bressler, you have a number

of backup slides, and I was wondering whether you have a slide like 78 which -- no, the one that you have up there -- which gives the same picture but tracks individual subgroups like women or individuals by age because, in some sense, the mean is misleading. There is a lot of variation in these trajectories over time, and we're here with the evidence from some subgroup analyses which shows that there may be different reactions from different types of people or different types of lesions.

DR. BRESSLER: So, specifically you would like to see the average visual acuity change or the distribution of the change by subgroups?

DR. KILPATRICK: I'd like to see a temporal distribution like that from baseline to month 12 of loss of visual acuity in subgroups because if we looked at individuals, it would be too messy I suppose. But do you have anything like that?

DR. CIOFFI: Neil, related to this --

DR. BRESSLER: Not specifically like that.

DR. CIOFFI: -- with particular attention to the better vision group versus the worst vision group because the people that were down around 20/200, which made up half the

population as pre-study stratified, did better as a group -- correct -- than the people with better vision.

DR. BRESSLER: They did better but both had a benefit.

DR. CIOFFI: Both had a benefit but the treatment benefit was markedly better in the people with worse vision. Without this time analysis that was just brought up by Jim, it may be this bottoming out phenomenon, and the reason that they do better as a group is because you can't go too much further.

DR. BRESSLER: We were able to measure confidently dropping at least 3 lines and 6 lines because we had the absolute worse vision at 20/200. Most of the cases weren't 20/200 then. They were 20/160 perhaps or 20/125 as well. That would mean we'd have to measure down to 20/400 to have a 3-line loss or 20/800 to have a 6-line loss, and we did have the ability to measure for that. So, the bottoming-out effect is not because of the measurement ability. It could be that patients with neovascular lesions don't often drop to those severe levels of vision, but they do so that we have that. I don't know if we have the individual visual acuity distributions by subgroup over time, though.

DR. SEDDON: Would it also be related to the fact

that the better vision group had less opportunity to really improve 3 lines because they didn't have as far to go, in other words, to improve.

DR. BRESSLER: Yes. They certainly can't improve as much necessarily.

DR. SEDDON: That might also, I think, explain the difference. There's a lot more of an interval envisioned for the individuals who have worse vision to begin with.

DR. BRESSLER: Yes.

Mohammad?

DR. AZAB: I just wanted to say that the prospective plan of the protocol was that all the subgroups would be looked at at the primary endpoint, which is the percentage of the patients who lost less than 15 letters. So, the subgroup analyses that we have are all looked at at the primary endpoint. These were the subgroups that were presented in the main presentation. You have the subgroups according to the VA stratum by age and by gender. We can quickly review that if we can have the main presentation slide 64 and all the next ones.

So, this is the subgroup. All of them are presented by the primary endpoint analysis which was the

prospective plan in the protocol. It was percentage of patients who lost less than 15 letters. This is the subgroup as Dr. Bressler presented, the two VA stratum, and I think we totally agree with Dr. Seddon's interpretation of that about the difference. But the most important is there is a consistent difference and in the same direction for the two subgroups.

Next slide. This is the subgroups for age. The same thing on the difference. There was a consistent difference in the two subgroups. There was an indication, as agreed with the FDA interpretation, that there is higher benefit in the patients less than 75.

But actually one interesting point, if you would be interested, if you're looking at the individual studies, because that was also raised, that difference in the two age subgroups was only present in one study, study A -- actually study B. The difference between verteporfin and placebo was a 15 percent difference in both groups. In the less than 75 and more than 75, they had exactly the same benefit in study B and they had less benefit in study A. So, that difference was not consistent. Actually, Dr. Chambers showed that slide in the bar chart that he had. So, overall both subgroups benefitted

from therapy.

The next one was I believe the gender information. The same thing. Consistent difference in the two subgroups of gender, as Dr. Bressler presented.

And the next one I think is the information on iris color, difference in the direction of benefit for the two subgroups of dark and light irides.

The next one is I believe the lesion size, and Dr. Seddon asked initially. There was actually no imbalances of any of these lesion sizes at baseline. They were all balanced between verteporfin and placebo, and as you can see here, once again as presented, the difference is in the same direction of treatment benefit for all different lesion sizes.

DR. FONG: It's 5 of 12:00. Should we continue or should we take a lunch break at this point? Why don't we take a lunch break for 45 minutes or an hour? An hour, okay. An hour and 5 minutes. We'll reconvene at 1 o'clock.

I wanted to remind the committee members not to talk about the issues being discussed today.

(Whereupon, at 11:55 a.m., the subcommittee was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:04 p.m.)

DR. FONG: Let's go ahead and get restarted. Welcome back from lunch. We're at the Ophthalmic Drugs Subcommittee of the Dermatologic and Ophthalmic Drugs Advisory Committee on Visudyne therapy.

I wanted to open the floor up for open discussion of the issues and also questions for both the sponsor and the FDA.

DR. CIOFFI: I'll start.

DR. FONG: Jack?

DR. CIOFFI: I have a more basic question about safety, and it might get at some of these other issues that came up earlier, and that is the predilection for this just going to new vessels. How do we know that? With the thought being that with all these retreatments, if it is somehow affecting other vessels there might be some danger to retreatment. How do we know about the new membranes? It's stated over and over, but the evidence for that we've never been shown.

DR. STRONG: We do know from preclinical studies, the angiographic studies have shown that there is selectivity for choroidal neovascularization. There may be some getting into the other nonproliferative vessels, and that seen by the nonselective events at the very high doses. The thing is that we do know that this therapy in the current regimen does work and that we get a good outcome.

DR. CIOFFI: But that still doesn't get out

whether or not, with recurrent dosages, you're going to be shutting down the fine capillary network of the choriocapillaris or even of the retina itself. So, I guess my question remains, how do we know that it's only concentrating in the neovascular nets?

DR. STRONG: We know that there's selectivity.

DR. CIOFFI: On what sort of order is that?

DR. STRONG: Julia, would you like to comment?

DR. LEVY: There is selectivity in terms of the absolute amount of drug that is taken up by proliferating tissues as opposed to tissues that are not proliferating as rapidly. This is mediated by the fact that the drug is distributed almost instantaneously to low density lipoproteins once it's introduced into the blood. Those cells which have an elevated level of LDL receptors take up between 5 and 10 times as much drug as is taken up by normal cells. This has been shown in many, many preclinical models, including tumor models, as well as neovascular models. Therefore, the finite amount of drug taken up by the neovascular endothelia is probably in that order of five times as much drug. You can see this by fluorescing the drugs at the time of administration. It's taken up very rapidly. Maximum uptake

is within 15 minutes. By measuring the light very carefully, you can therefore have a very large safety margin between damaging normal vessels and abnormal ones.

DR. FONG: Before you go, can you identify yourself for the record?

DR. LEVY: Yes. I'm Dr. Julia Levy. I'm the CEO of QLT.

DR. FONG: Dr. Herndon?

DR. HERNDON: I have a question perhaps for Dr. Azab regarding photosensitivity. A two part question. Number one, if you can go into more detail, what kind of reactions you were seeing with your photosensitivity, particularly the more severe photosensitivity reactions.

And number two, how do you advise your patients prior to their beginning the study as far as precautions to take?

And another question I should throw in as well. When you see these photosensitivity reactions, do you see them more likely with people who have had further treatment options, or is there a dose response to further treatments?

DR. AZAB: Can I have the photosensitivity slides, starting with 329, please?

This just gives a brief introduction to the details of the photosensitivity that would answer your question, Dr. Herndon. The first is just the details of some of the bullet points that were on the summary slide that I presented. So, these are the details of these data.

This is just the evaluation of the pharmacokinetics of the drug. Although you would see that there are slight differences between 3, 6, and 14 milligrams per meter squared, and these are high doses. These are more than double the dose recommended, which is 6 milligrams per meter squared. And all of them, the last detectable concentration, are well below the 2-day period, well below the 48 hours. These are mean concentrations. But as I said also, there were no individual concentrations that were measurable beyond 48 hours.

The other piece of data that I showed just a summary of is the DK of skin photosensitivity. There was a very rigorous skin photosensitivity testing done in one of the skin cancer trials, trial BPD001. What we've done is that for patients, we evaluated their minimal erythematous dose, which is the dose of light that is capable of producing minimal erythema, to define this as their baseline photosensitivity

before taking any drug. And then after taking the drug, at different doses we evaluated when they're going to get back to that baseline minimal erythematous dose.

These are the different doses. Luckily in this trial we went up to the dose of 20 milligrams per meter squared, so that's more than triple the recommended dose that we have for the ocular indication. As you can see, as you go to the highest dose, this represents the 5-day period. This line is the baseline minimal erythematous dose. So, when they go back to this line, they go back to their baseline photosensitivity of their skin. As you can see, all of them go back within 5 days at the highest dose. At the lowest dose, which is the 6 milligrams per meter squared, which is the recommended dose, all of them go back within 48 hours.

Now, the next slide would give the information on the details of all the skin photosensitivity reactions that we have. As I said, the patient is at risk of developing the photosensitivity reaction at every treatment course. So, really the denominator for the incidence of these reactions is the number of courses, not the number of patients. From 1,790 courses, these are all the photosensitivity reactions that were reported in the study.

These are what actually happened to the patient in each of studies A and B, and as you can see here, we have indicated the course where this happened and also the day when this happened.

There were a couple of reactions that were not included in the verteporfin related reactions. I would like to point to the committee where these are. This one, because this one occurred 90 days after verteporfin. It was clearly related to a fluorescein injection before the patient receives any verteporfin. The other then that was not related was a nonspecific term that was used by the investigator of red inflamed skin that described a reaction that was described by the investigator as something that is definitely not related to treatment. As you can see also, there is no temporal relation to that. It happened day 40 after treatment.

All the others, as you can see, occurred at day 0 or day 1 with the exception of the two events that I mentioned that occurred at day 3. Both were mild and both represented a skin rash. One has a skin rash of an area exposed to the sun, and the other one at day 3. This one had sunburned knuckles.

If you can see, all of them represent mild to moderate reactions. All of them are described as sunburn,

which is the usual reaction that you will get from being photosensitive to a drug. So, all of them are really nonspecific erythema or sunburn, and all of them were mild to moderate.

Now, the two severe reactions -- actually these were two once again from the overall 1,790 treatment courses. Actually we have documentation of actually what happened to the patients. It's interesting to note both of them occurred because the patient exposed to sun almost immediately after treatment.

One of them -- it was not the systemic photosensitivity. This event actually occurred from an extravasation of the drug, and the patient immediately after treatment, which had extravasated, exposed that area to the sun. So, that of course was a severe reaction. Certainly we do have a long list of instructions in both the protocol and in the labeling to try to prevent that.

The other patient who had the severe reaction was a patient that we have documented also immediately after the injection, went and exposed to the sun for several hours. So, severe reactions only occur if the patient exposed themselves to the sun almost immediately after injection without really

paying attention to the instructions.

As I said, these are two events from almost 2,000 courses, a chance of about 1 in 1,000. In terms of compliance, we have done everything possible to try to educate the patients about this, and I think the fact that these, as little as they are, is an indication that there has been a very good compliance from the patients in terms of protecting themselves from the sun.

We had discussed this extensively in the company, and we have actually designed a full education training program for the physicians and an educational program for the patients to educate them on the fact that they need to protect themselves from the sun.

I believe Dr. Rosenfeld would like to make a comment too from his personal experience.

DR. HERNDON: I have another question too along the same lines. There are other ways to measure things that are happening in the macula, OCT being one. What do you tell patients whose physician may want to follow their lesions with OCT or provide some other modalities to assess the nerve fiber layer or the retina?

DR. AZAB: Would you like to address that, Dr.

Rosenfeld or Dr. Bressler?

DR. ROSENFELD: I would like to comment just briefly about your concern regarding photosensitivity. When patients come in and receive treatment, they're also educated as to the need to avoid direct sunlight and bright lights for 48 hours in the TAP program following treatment. Patients were given dark glasses. They were all wearing wide-brim hats, long sleeves, and long pants when they left the hospital. We were particularly concerned about this being in Miami, Florida, being appropriately called the Sunshine State. We were worried that sun exposure could result in some photosensitivity reactions, which were not a problem.

Regarding your question about ancillary studies, regarding OCT, we generally do not recommend any additional studies be done within the first week after fluorescein angiography. I know additional ancillary studies are some things that many centers are interested in doing to further evaluate how this drug works and how we can improve and enhance the treatment. But currently those ancillary studies were not done.

DR. FONG: Dr. Seddon?

DR. SEDDON: Yes. As Dr. Chambers presented,

there's an increase or trend for an increase in creatinine and SGOT and SGPT levels. I wondered if we could discuss that a bit, and also is there any evidence in any related studies for liver or kidney dysfunction?

DR. CIOFFI: Actually I was going to ask the same question as well. The creatinine level was 5-fold. Although the numbers are very small, it was 5-fold more likely in the treatment group. If we could just add on to the question how do you plan to follow that up with your ongoing studies.

DR. FONG: Let me just interrupt. I wanted to remind everybody to say their name for the record so that the transcriptionist can note it.

DR. AZAB: Can I have 338 please?

Just a reminder to start the discussion about these abnormalities, patients were supposed to have the laboratory measurements, and these events that were reported as adverse events were things that the investigator recorded as a laboratory abnormality. We would expect in patients in this population will have some laboratory abnormalities, but this could vary from very small changes of their hemoglobin, hematocrit in this study and creatinine to very wide ranges.

So, this slides shows, first addressing the issue

of anemia, combining the data from both studies A and B. As you can see, this is the total and this is the intensity of the event. The total number of the events -- it's very important to be reminded that the trial has a 2 to 1 randomization ratio. So, you always expect that there will be a double number of any verteporfin patients. So, the most appropriate is to look at the percentages. There were 3.2 percent in verteporfin, 1.9 percent in the placebo group that reported anemia. As you can see, there was only one case of severe anemia that was reported. Actually we will see the outcome of these patients as well.

Of course, we were mainly interested in looking at the clinical difference and clinical significance, but just for information, this of course is not statistically significant.

These were the three cases, two reported as moderate, and one reported as severe. Once again, in all our experience from the phase III studies, only 3 cases. The relationships were unknown, not related, and one the investigator said that this is possible. If we look at the course and day of onset, it occurred about 3 months after the injection of the drug. All of them either resolved or

improved. The one at the data set was unchanged at the time of the submission. That event actually occurred almost 9 months after treatment. So, it's very highly unlikely that it was caused by the drug.

One thing that I forgot to mention in the beginning, that this class of drugs, verteporfin and most of the photosensitizers, are really pharmacologically inactive drugs until they're activated by light. There is really no evidence from any animal data or from the other first generation photosensitizers that there is any effect on hematological or renal function.

Can I address the creatinine in the next slide, please?

The picture of the serum creatinine, these slides would show once again the total serum creatinine and the severity. There was none which was recorded as severe, and most of the events -- all the events actually -- not most -- were recorded on mild to moderate.

I do have a slide actually showing the actual values of creatinine. This slide shows that all the patients who reported elevation of creatinine at month 12, at month 18 had their creatinine going back to normal despite continuous

treatment. So, if there was really a toxic effect of the drug, with continued treatment you would expect that the creatinine would remain stable or would go up. Actually it went down in all the patients for whom we have long-term data.

Unlike the efficacy data, which just looked until the 12 months, as I said in my presentation, the safety data that we had beyond 12 months are included here. That's why actually we do have, in terms of adverse events numbers, events up to month 18 and very few up to month 21 as part of the submission.

I can give you the numbers of the creatinine and anemia because I have them here. The creatinine cases by severity, there were 3 percent and 1.4 percent mild. There were .5 percent, 2 cases, and none in placebo. And there were none which were severe events in creatinine. That was a total of 3.5 percent and 1.4 percent. Once again, the p value is .2.

Just for information, there were 10 cases which had an invasion of serum creatinine at month 12 for whom we had 5 patients who had their follow-up at month 18 and all of the 5, their creatinine turned back to levels below the levels that we had on month 12 despite continuing treatment.

DR. CIOFFI: But not normal?

DR. AZAB: Well, I can give you the actual values. Most of the patients at this age, as you know, start with borderline serum creatinine. So, all of them are in the upper -- just around 100.

The patient had baseline 84, went to 93 at month 12 when they reported as an adverse event. So, that went from 84 to 93. Actually many of our labs consider that still normal. It went back at month 18 to 91.

At baseline, the other patient was 97. Was reported as an adverse event when it went up to 126, and then after that it went to 104.

The third patient was 97 at baseline, reported as an adverse event when it went from 97 to 105, and then came back to 97 which is exactly the baseline value for the patient. That's another patient.

One patient was 134 at baseline. So, really that was abnormal, went up to 151 when the event was reported, and came back to 142 despite continuing treatment.

The last patient was measured in milligram per deciliter so the units are slightly different. It's 1.4, went up to 1.7 when the event was reported, and came back again to

1.3 which is actually lower than the baseline value.

So, we really believe, having looked at this data extensively and knowing this class of drug, that there is really no evidence of changes in hematological or renal parameters.

DR. FONG: Johanna?

DR. SEDDON: I know the numbers are small, but were there any common themes in the series of patients with abnormal values in terms of predisposing medical conditions such that you might want to caution the use of this medication in certain patients, or do you think it was not related at all?

DR. AZAB: Looking at all the events, the interpretation that we have is, as you see in the figures that I mentioned, these are all variations of lab values. Whenever you measure lab values at different time points, you get some variations. Some centers reported that as adverse events, and these are the figures that we're dealing with today. But looking at the follow-up of these adverse events, they really all resolve despite continuing treatment, which we think provides strong evidence that it's not really related to the drug. As I said, there's nothing in the mechanism of the drug

that leads us to believe that there is any effect on anemia, creatinine.

The numbers are extremely small. As we see, we have this 1 and 2 percent difference. There were about 10 other events or from 10 to 14 other events which happened at a higher incidence in placebo, and the difference that was higher in placebo was between 2 and 4 percent higher than verteporfin. Of course, we can't make the argument that this means that the placebo is causing some of these other events, but the key message is that all these differences were small.

The only factor that we found, which was interesting, but I don't really think it explains the matter, but most of these events we tracked down to one center in one study. If you look at study B, the percentages are identical for anemia and creatinine. The percentages are slightly different for study A, and that drives the total population. We tracked most of these differences in study A to one center who used to report a lot of these minor variations as an adverse event. Now, of course, it still doesn't explain why they're slightly higher with verteporfin, but we believe that this is just a random variation.

DR. CIOFFI: Staying on safety, the one event

that you did present that was slightly greater than 13 percent was injection site events.

DR. AZAB: Correct.

DR. CIOFFI: Is there any repetitive nature to that? Does a patient that reacts once -- does that predict that they're going to react again, or was this more to do with the IV site itself? Or can you explain?

DR. AZAB: That's a good question. We also looked at safety in this data that's summarized in the briefing document but not presented today. But we also looked at the incidence of adverse events over time by course to see if there's any trend of increasing adverse events or any safety issues increasing over time. Actually there was quite the opposite. The trend was for most adverse events to be reported early, and we believe that as the patients and the physicians get more experience, actually there was lower incidence of adverse events being reported over time, which was a good safety reassurance for us.

For the injection site reactions, that's exactly what happened. As the centers gained more experience with the injections, the incidence of injection site reactions dropped. There was absolutely no prediction that if a patient gets a

reaction, that he will get it next time. It's most likely that they will never get it again because the physician now or the setting for the intravenous procedure had been very strict and they enforced the routine procedures that they should do. So, there was actually quite the opposite. We have indication, when we looked at it by course, that the incidence of these reactions drops.

Once again, we tracked these back to find out any predictable factors so that we can use it for the educational material for patients. We found that most of these reactions come from the fact that some physicians, despite the instructions in the protocol, use very small needles, the butterfly needles, in very small veins in the back of the hands. With this patient population with their fragile veins, actually most of the injection site reactions, especially the severe ones, occurred when using very small needles in very small veins.

That's why I raised the issue in the safety presentation that we are enforcing the message in the educational material and putting that in the label that the physician should really apply strict intravenous procedures and should avoid the small veins in the back of the hands and

using large veins.

One interesting fact about the safety that was not the subject of today in the ocular trials, but for example, the pharmacokinetic trials which were, as you know, all are done in institutions which are very familiar with intravenous procedures and with pharmacokinetics. We have 73 subjects receiving these injections. We don't have a single intravenous injection reaction from the pharmacokinetic study in 73 subjects. Of course, they were younger patients and it was done in institutions very familiar with IV procedures. But once again, it indicates that these reactions are probably, at least some of them, preventable if we really follow strict procedures for these patients and being more careful.

DR. FONG: I have a question. What I said before was that I thought that the treatment benefit is relatively moderate and the effect appears to be temporary. My concerns have to do with the safety of this drug, both ocular and systemic. Has there been any other experience with this drug? This drug is a new molecular entity. Am I correct? There has been nothing else that's been approved for this related?

DR. CHAMBERS: That's correct.

DR. FONG: So, for a totally new molecular entity, I'm just concerned about what the adverse effects are. Is there any data from the other trials? I know you've done some trials outside the U.S. Is there any data from approval meetings from Europe about the safety of this compound?

DR. AZAB: As mentioned, we have extensively studied this molecule in different indications. Of course, a lot of healthy volunteers received this molecule without the light. So, that addresses systemic safety. We had studies in psoriasis and skin cancer patients, and of course, we have the ocular trials. All this material was submitted in the NDA for review.

Actually all the systemic events in all the other trials were lower than the ocular trials, and we interpret that by the difference in mean age of the patients. In the pharmacokinetics studies, there were healthy, young volunteers. In the dermatology studies, the mean age was about 50 years old, between 50 and 54. The mean age for the ocular trials was 75. So, the fact that there was a higher incidence in the ocular trials actually relates to the age.

What is interesting -- and that the good thing about running randomized, placebo-controlled, masked trials --

is if you look at all the systemic safety and all the ocular safety, the incidence of any adverse events which are shown in one of the slides here -- and maybe we can bring up the slide on the main presentation on the overview of safety. There was an incidence of 83 percent -- any patient who reported any adverse event, ocular or systemic -- in verteporfin and 86 percent in placebo. So, that global measure already indicates that there are really no safety concerns with this molecule. We've also looked at the different body systems that I have shown there, and there was no indication of any difference in the incidence of adverse events in any one of the body systems. So, that's the slide that we have from the main presentation where you can see incidence of any adverse events was about 83 percent in verteporfin, 86 percent in placebo.

I think the most important factor that we always take a look at is how about the withdrawals due to adverse events because this indicates that if the patient is really having something of concern, that the physician has to stop treatment. Once again, the incidence was small. Most of these were the ocular events that we have discussed because we indicated to physicians that if a patient has a severe vision decrease, we should stop treatment until the vision recovers.

In the protocols, they should have stopped treatment. And also some of the ocular events like the vitreous hemorrhage that I've shown -- most of these are indicated in these withdrawals, 2.7 percent, and placebo also had 1 patient withdraw, .5 percent. Always there was a 2 to 1 randomization ratio.

If we look at any other serious adverse events, which would address really any concern of serious events of any kind, once again it's almost identical between the two studies. It's 16 percent and 17 percent between verteporfin and placebo.

If I can go back to the backup slide 324, please. This runs over the all body systems that we've presented. Once again, we wanted to look at the clinical differences, but at the same time for information, we've conducted statistical analysis for any p value just looking for any trend. As you can see here, these are all the body systems that are coded in the dictionary for our evaluation of adverse events. None of these differences was statistically significant and none of them looked to us as clinically significant.

As I've shown in the slide in the main presentation, there were four body systems where numerically

that number was higher than that number, but there were seven other body systems where that number was higher than verteporfin. We believe once again that these were normal variations of reporting adverse events, but to our interpretation, for a systemic drug this is an extremely well tolerated drug especially considering the mean age of the patient population treated in these trials.

Dr. Bressler, you want to make a comment?

DR. BRESSLER: I was just going to expand, Don. Number one, when we see a benefit, whatever this benefit was and whatever qualifier you want to put on it in terms of having 28 percent difference for that primary endpoint, we of course then want to know, well, is it safe in this patient population. I for one was always concerned -- more trepidation when you're dealing with an average age group that is in their mid-70's, as this was. So far, it appeared remarkably safe. There are exceptions that are listed here.

Then you have to worry about the unknown. Okay, it's safe for 1 year. What about if someone does need 3, 4, 5, 6, 8 applications? We don't have a lot of that information yet systemically, but Mohammad's data, it is worth emphasizing, is any of these events even beyond the 1-year

follow-up. Anything that we had, even if someone had 15 or 18 or 21-month follow-up, at the time that we had the entire study group followed for at least 1 year. Since they didn't all come in at the same day, we do have this longer-term follow-up included in this safety analysis systemically.

Now, ocularly we only have the vision data out to 1 year. So, the question is, is there some delayed reaction? Is there some atrophy that's going to cause problems later on? This was also alluded to when they said, how do you know it doesn't cause more damage? I just know it causes less damage out to 1 year in the treated eyes than if you leave them alone, because leaving it alone, the disease is so bad.

The data and safety monitoring committee does look at data beyond that. I don't think they can share the details that they have, but I'd like to ask Lee Jampol, if I could, to just comment on what information he knows in general about ocular safety. Does this cause vision damage in general to whatever they have to 18 months or something? Because that also would give you more confidence in do we have longer safety or not. So, Lee, did you want to comment just from the data monitoring committee?

DR. JAMPOL: My name is Lee Jampol and I'm

Professor and Chairman of Ophthalmology at Northwestern University in Chicago, and I'm a member of the data monitoring committee which functions as an independent monitor of the safety and efficacy in the study. I don't play any role in the presentation today.

But there have been several times when the point about efficacy beyond 1 year has been brought up and about toxicity beyond 1 year. I have no data for you, but I can tell you that the data monitoring committee has monitored a considerable amount of data at 15 months and at 18 months and some data beyond that. I'm authorized to tell you that there's no evidence of a loss of efficacy of the treatment up to that time, nor is there evidence of the toxicities that you're concerned about, either systemically or locally. So, that might be somewhat helpful to you without data.

DR. FONG: Wiley, has the FDA seen the 2-year data? Have they seen any brief analysis of this 2-year data? It seems to me the job would be a lot easier if we had this 2-year data.

DR. CHAMBERS: The cutoff on the safety data is at a later particular point, and depending on when people happen to enroll, there are people that went all the way

through to 2 years. There are people that did not go as far. The basic breakdown in the data that we had -- and that includes some efficacy information -- was we had everybody at 12 months. At 15 months, it was approximately half of the people had gone through 15 months. At 18 months, it was approximately a quarter. At 21 months, it was approximately an eighth. It basically fell off as you went down. It's not that there was no data. They were not complete data sets, and there's always the question about what the selection is when you're looking at those particular things.

There have not been signals in any of the things that we've seen of any data later on, but the numbers are small.

MR. MANDT: If I could just add a comment to this. The company is in the process of preparing the safety update which we're required to provide before FDA makes a final decision on the application. That's going to be submitted to FDA within the next 2 weeks or so. So, there will be more information that will be provided.

DR. CHAMBERS: That's safety, though. It's not efficacy.

MR. MANDT: Correct.

DR. FONG: Let me just follow up with one question for Dr. Jampol. That 2-year data, that's the full 2-year data set that you've looked at?

DR. JAMPOL: No. You misunderstood me. We have not seen very much 2-year data. We've seen a large amount of data at 15 months and at 18 months and then some data beyond that. At our last meeting, we reviewed that and we discussed that, and it was clear to us that there was no evidence of decline in efficacy at that point.

DR. FONG: Neil, it seems like visual acuity is a fairly straightforward endpoint. Nobody has looked at that at all? I mean, that's something that doesn't need much analysis. It seems like you would have that available for discussion.

DR. BRESSLER: The visual acuity data is what Lee is referring to that they looked at. The prospectively planned analysis was that we would look at it at 1 year, present that data to the FDA, and then look at it at 2 years because it wasn't likely things were going to keep changing back and forth, back and forth. From a safety standpoint, we wanted the DSMC to look every 6 months in case there was a clue that something is reversing down the line.

So, it is sort of easy to look at visual acuity, on the one hand, but I can tell you preparing this visual acuity in these 600 patients at 1 year even was an enormous effort. So, it isn't so easy to put together 24-month just visual acuity data. It does take a bit and it's not all in yet, so we can't do that.

But again, I would summarize by saying the evidence is clear at 1 year and then we ask ourselves is there any reason we think this could reverse. Well, there are some unknown reasons that it could, but we didn't see anything out to at least 1 year to suggest it would reverse. And then I know that we've had the data monitoring committee continue to look at that data, and as Lee suggested, he still doesn't see any surprises to suggest that there will be a reversal.

That doesn't mean there won't be at 2 years some unbelievable trend that happens to reverse it, but we just don't see it yet. We're concerned that it could happen theoretically because it could be that there's some delay to the photoreceptors or whatever, and maybe that happens at 3 years or at 5 years or at 8 years. But to the best of our knowledge, this benefit at 1 year appears that it likely would then continue into our second year unless some unknown factor

that we haven't thought about reverses it.

I do think it's appropriate for the FDA to then say, okay, whatever we do with this, we still need that 2-year data so we can complete the story. So, I do think that's appropriate, but I also think it's appropriate to make some general decision in the interim for 1-year data given the impact this has on visual acuity and the number of people getting that each year.

DR. CIOFFI: Dr. Bressler, this is Jack Cioffi. On a related issue, actually in the review that the company provided us on page 26, there's a set of Kaplan-Meier curves. They have it for the overall study and also for the subgroup analysis. In both groups actually, there really appears to be a time lag of about 6 months, 3 to 6 months, in patients until they go to approximately a 20/200 level. So, you keep on talking about the clinically significant vision saving that's going on, but really isn't this the issue? And maybe you could comment on the clinical significance of the 6-month grace period, if you will, before these patients go on to 20/200.

DR. BRESSLER: I think it's a representative average again. I look at this like we look at average visual

acuity where you see the entire group is deteriorating, but not as great as if you left them alone. Within that entire group, there are people that at 3 months or 6 months or out to 9 months, 12 months, some 15 or 18 months are then preserved at a certain level. So, I think this tells us that overall there's a continued decline going on in both groups on average, but it's not the entire population so that you should tell a person this will reduce your chance of losing vision. It doesn't guarantee. For each person that loses vision, it's added into that survival curve that they've now lost vision.

To me the translation of this is if you have a person, for example, that stops deteriorating at 3 months or 6 months and doesn't deteriorate until 18 months or something, that's a benefit for that person for that short period of time.

DR. FONG: Dr. Seddon?

DR. SEDDON: I'd just like to go back again to the discussion on side effects. So, my understanding from the data that were presented then is there should be no medical or systemic contraindication at all to the use of this drug. Is that correct? Based on the available evidence, there should be no contraindication?

DR. BRESSLER: I'm going to let Dr. Azab still handle the medical related questions.

DR. AZAB: There are really no relevant contraindications, but there are some specific contraindications that for medical and regulatory issues we put there. The ones that are in the label and shared with the FDA were the ones for this class. This is a porphyrin and there are people that seem to be allergic to porphyrins. So, it's contraindicated to patients who are known to be allergic to any of the components of the drug injection, and also patients with porphyria because patients with porphyria would be highly sensitive to this. We have not studied that. It's a generic contraindication to this class of drug. It is not really a contraindication that is specific for verteporfin.

DR. SEDDON: Will be there any warning at all about elevated creatinine or SGOT, SGPT prior to the use of the drug in terms of taking precaution in those patients? Or do you feel that that's not necessary?

DR. AZAB: Usually the process for the label is that we have put a very identical list of events that happened in any numerical high percentage in the verteporfin group even if it's a .5 or .6 percent difference. We put that in the

list of potential adverse events. I think the list that we've discussed and submitted to the FDA are almost very similar. We put all these as potential adverse events.

Dr. Chambers, do you want to comment?

DR. CHAMBERS: That's one of the things that the agency is interested in comments from the advisory committee on, the labeling aspects that you think should be placed in the label.

DR. SEDDON: That will be decided here or discussed here?

DR. CHAMBERS: If you have suggestions, we would like to hear them.

DR. SEDDON: Well, it does seem reasonable to list the adverse events that have occurred on the label.

DR. CHAMBERS: Just listing the adverse events will happen. There's no question these things will -- certainly anything that was above a placebo rate unquestionably will get listed in the adverse reaction section. The question would be whether we add anything else to either the precaution or warnings section of the label. The usual assumption in a precaution is that there's something you can do something about.

DR. SEDDON: I think that decision would be greatly aided by having the follow-up from 18 months and from 24 months. But I think this is certainly something that is worth noting and perhaps should be in the warning label.

DR. CHAMBERS: In addition, not just this product but all products gain additional history as they are marketed. The agency reviews the adverse reactions that are reported both at the time of approval, subsequent studies and subsequent marketing, and does frequently alter the label of products. You should not assume that the labeling that went out at the time of original approval is the same a year or two later as we learn more information.

DR. SEDDON: I think photosensitivity and these abnormal blood tests should be listed as potential contraindications to the use of this medication.

DR. CIOFFI: I'm not sure I agree with that. I think listing, as you said, just running the list of adverse events that occur more with the drug than with the placebo is one thing. I think the company has done a good job at following up on the creatinine levels, and they seem to balance just above and below abnormal or normal. I think they followed up well on the other. I think they should continue

that, but I'm not sure that we have any evidence to show us that we should put an actual contraindication for some sort of hematologic or renal function measure.

MR. MANDT: Dr. Fong, could I add one comment?

DR. FONG: Please.

MR. MANDT: Just to address the longer-term issue and not having the 18- or the 24-month data, in two different places in the PI we have proposed having a statement that says long-term effects are not known at this point. So, there will be two places in the PI where that will be disclosed.

DR. CHAMBERS: One of the other things, though, for consideration is that it's probably not in the patient's best interest to be on another photosensitizing agent at the time that you have therapy. The expectation is there would be some discussion in the label about not compiling multiple photosensitizing agents.

DR. FONG: Dr. Kilpatrick?

DR. KILPATRICK: Also, I'd like to hear the committee's response to the 3-day window under which patients are supposed to be kept out of sunlight or other radiation.

DR. FONG: The committee's or the sponsor's?

DR. KILPATRICK: The committee. I'm not

qualified to speak, but I feel that the evidence for 3 days is based on young, healthy volunteers, and although I know that the half-life here is short, we're dealing with an elderly population and I don't know the biology of it.

Dr. Azab wants to talk.

DR. FONG: Go ahead. Please state your name again.

DR. AZAB: Mohammad Azab, Clinical Research, QLT PhotoTherapeutics.

The slide that I've shown on all the photosensitivity reactions, these were the ocular trials patients. These were all the patients from the trial, the relevant patient population. As I indicated, there were 10 reactions in the 1,790 treatment courses that were given. None of the reactions occurred beyond day 3. All of them, except 2, occurred within the first 2 days. So, I totally agree that we shouldn't stop the evaluation by looking at just the PK in healthy volunteers. That's why we looked at each single one of them to identify when it happened and how it happened. Also I explained the origin of the two severe events that occurred just immediately after the injection.

DR. KILPATRICK: With respect, sir, you used the

word "population." If this is marketed, it will go out to a very general population which is much larger and not necessarily representative of the group that you've been studying. So, my concern is about the untypical patient or situation not simply being in Florida but other situations.

DR. AZAB: I agree all clinical trials are in an artificial setting. When you do a clinical trial, you have a patient population. The belief from the patients' characteristics that we had in the trials -- it's in the briefing document and we can share with you -- is that the patients' characteristics that were included in the trials were reasonably representative of the patient population with neovascular AMD and predominantly classic, but that's as far as we can go. I totally agree with your point.

DR. FONG: I have a question for Dr. Chambers. Given that the treatment effect here is modest and it's temporary and the long-term effects still are being debated, is there any mechanism for expanded access of this drug to patients short of approval, or are there other avenues?

DR. CHAMBERS: Short of approval, there are additional avenues such as a treatment IND which the company has already undertaken. It should still be remembered,

though, even under a treatment IND that's not as easy an access for the vast majority of patients. It is still limited as far as the number of sites where individuals can go and you are basically then preselecting individual physicians, which is not necessarily the same as the individual patient's normal ophthalmologist that they are following or normal referral pattern.

A treatment IND has generally been felt to be helpful in providing a therapy while review was ongoing but is not expected to continue long past the review process. So, if you really want wide access, the mechanism is approval.

DR. FONG: What about the possibility of a treatment IND until the 2-year data are available? Is that something that precedent has been set on or people have done before?

DR. CHAMBERS: Any of those things is possible. It's a matter of whether there is a belief whether the benefits outweigh the risk at whatever particular point in time and whether you feel your recommendation and the agency's conclusions of whether there is a benefit that should be approved now or whether it's necessary to go and wait.

DR. FONG: I was just looking over the draft

questions, which we'll talk about in a little bit. Is that one of the questions you want us to address whether we want to vote for approval? Because it's not specifically listed. And if so, is treatment IND also going to be part of the questions that you want us to address?

DR. CHAMBERS: The questions didn't specifically talk about approval. As you know, there is information going on from the 2-year trial. The question was how much weight necessarily to put on the 2-year trial, but even more importantly, should we be encouraging longer trials than 2 years, not necessarily waiting for approval in either case for the 2 years or beyond, but based on what you've seen and based on your clinical experience.

You have to remember that at the time the various discussions went on with the company -- not just this company, but other companies developing this -- there was not even the information that you see now. So, it was experts' best guess that 2 years was a relevant particular point of time and that clinical benefits at 1 year were relevant. They are based on the knowledge we had at the particular time. That was a couple years ago. As we learn more, we adapt.

DR. FONG: Dr. Kilpatrick?

DR. KILPATRICK: It might be appropriate for me to voice a concern that I have apropos of what Dr. Chambers has been saying. I'm concerned that an important scientific principle is being eroded here. Forgive me if I sound like a professor, which I am.

Phase I and phase II studies are by their nature exploratory. A phase III study is by its nature confirmatory, randomized clinical trials which are designed to test explicitly stated hypotheses. Phase IV studies are largely follow-up, post-approval to establish long-term safety.

Now, here what we have in this situation is two phase III trials in which we're relying -- an undue reliance in my opinion -- on the p values of subgroup analyses which are at best exploratory in nature. They, for example, don't have the power, as Dr. Chambers has pointed out, to detect important differences, and we also have the problem of multiple tests of significance which are not addressed.

So, in my view this information can at best serve as the material in terms of pilot studies for future focused randomized clinical trials. So, I am leaning towards the implicit suggestion by Dr. Chambers that what we need here is a spectrum of studies targeted to confirm some of the

observations that have come out of this subgroup analysis.

DR. FONG: Dr. Chambers?

DR. CHAMBERS: One of the difficulties in studying diseases which have relatively slow progression -- and macular degeneration is not unique in this aspect. The one that obviously comes immediately to mind is also glaucoma -- is that you cannot run the number of pilot trials early on, get an answer, and redesign, if anybody expects to have any products developed in any of our lifetimes. We have to take gambles at what we think are the best endpoints and the best times to go and look at them at some point in time based on everybody's best knowledge. We carry them out. Obviously, there will be refinements as we go on later on, but you have to remember these calls were all made several years ago. If we think we don't have enough information now or have limited information now, everybody should realize how much information we had at the time that we were forced to go and make those calls. There really is not another option at the present time.

DR. CIOFFI: Although we're being asked to recommend or suggest approval or not, we're basing that I think on the overall study population. Where the

subpopulation analysis comes into play mainly is in a recommendation for an altered labeling, not for approval I don't think. Whether we like it or not, once this is in the hands of physicians, they're going to apply it how they see fit. I'm not as concerned about the subgroup analysis because it's only a portion of it.

DR. FONG: Dr. Jampol?

DR. JAMPOL: Yes. I'd like to comment on your statement about the 1-year data. In our estimate, the data monitoring committee, the study was very well powered, in fact, over-powered because of the necessity for two separate trials. Because the trials were so similar, combination of the data is very appealing. Because of that, this subgroup that you're talking about, greater than 50 percent classic, is a huge subgroup with a very consistent response to the therapy.

Subgroup analyses can lead you down some big mistakes, but it was our feeling that the numbers here were so large and the difference between the subgroups was so dramatic and consistent that we didn't have any trouble accepting the fact that in a sense the efficacy was identified retrospectively.

DR. KILPATRICK: Dr. Fong, I'd like to come back on that.

Thank you, sir. I have no problem with what I think was the primary aim of the two phase III studies to indicate and have found a statistically significant difference in predominantly classical CNV under the two treatment regimes. My concern is about the other subgroup analyses by different age groups, by women. Although we have heard various analyses, both univariate and multivariate in terms of logistic analysis, I'm not sure that those were powered to answer the questions that the data was being asked to yield.

Part of this is tied up with your concern, Dr. Fong, about the fact that we have a modest treatment effect in a very serious condition with lots of variability. I'm struggling here to suggest -- and the sponsors have made some comment about this -- that maybe we need a more focused, targeted therapy. What that is no one knows, however.

DR. FONG: I have another question for the sponsor. Dr. Chambers presented the health-related quality of life studies and showed to us that the benefits were in favor of the placebo group. I wanted to hear the sponsors address that and what they thought the reasons might be.

Also, I don't completely agree that it was multiple testing involved because from the NEIVFQ studies we know that distance vision and near vision are the main scales that patients with AMD are going to have problems with. So, Neil?

DR. BRESSLER: I would say we don't know anything more now than we did before the study was done in terms of quality of life because with only 89 patients selected out who had this questionnaire so far, we don't have the ability to make any sort of comment even if you find something that's statistically significant. We didn't have this for everyone because the instrument, the NEIVFQ, wasn't even published to be validated until after we started enrolling the patients. It's only been validated in English at that time, and we did this in many centers, both English speaking and non-English speaking, for both study A and study B.

But we did this in order to be able to gain some familiarity with incorporating this sort of instrument so that as we foresaw that additional studies do need to be done, we do need better treatments for this, if we can. We had none so far. Now we have something. If we see that we're going to be doing some in the future, we thought it was good as an

investigative group to learn how to incorporate these sort of instruments to gain additional data beyond that. So, this was more an internal exploration to be able to learn more about this, and I would wait till we have more information.

For example, if the second eye was the eye being affected by the disease, this alone could mess up your interpretations. So, if you figure out the first eye versus second eye, cut those numbers in half already, and say, okay, well, maybe we're dealing with even smaller ones. And then if there are other factors that affect the outcome like the lesion component or other factors that may have some impact on it, like the age or gender of the patient, if you can't control for those as well, you also have problems.

So, with just a handful of patients, I would say we don't know anything yet, and I doubt we would have presented that information as any reason to figure out how to label this versus not how to label it even if we found something positive in the other direction because it's just too small a number.

DR. FONG: It's interesting you should say cut it by half. The original designers sort of talk about a numeric change of 3 as being clinically significant. We're seeing

changes of 7 here in favor of the placebo group in the near vision and distance vision.

DR. BRESSLER: No, no, no. I meant I don't know how many numbers we're dealing with if, for example, one group has more of their second eye involved and one has their first eye involved. So, I wasn't talking about how to adjust the numbers. I was saying how many numbers we actually have to be able to evaluate. Clearly if you did 3 patients and you found 2 of them had a big change and 1 didn't, that wouldn't give me faith either in terms of what we found.

Mohammad?

DR. AZAB: Can I have 271, please? I just wanted to clarify the situation of the quality of life data.

As you know, these trials were done in 609 patients. This slide shows what we have done just to clarify the weight that we want to give to this data. Of course, at the time when we started the trial, we didn't start a quality of life because the VFQ25 hadn't been validated yet, was validated during the conduct of the study. So, the company tried to introduce that, and unfortunately, that came late. So, we used the validated question, but by the time that the trial had finished enrollment, only 89 patients had been

enrolled in the quality of life from 609 patients. So, that's a very small fraction of the patients that we have on the trial. These were the patients who had baseline and 12 months' evaluation.

As you know -- and Dr. Seddon had published and other members of the committee had published on the quality of life -- it is very important that we look if the study eyes were the better seeing eye because that's where you get the effect on the visual function in terms of quality of life. So, actually from these 89, only 39 study eyes were the better seeing eye, which further reduces the value of the data from the quality of life.

There was no treatment benefit on visual acuity global score. There were, as you know, several scales of this analysis with the factor that Dr. Chambers alluded to in terms of multiple analysis of multiple scales. The data was really inadequate to draw any conclusion because of these small numbers compared to the total number of the population.

But what was very compelling in the data is that looking at this cohort of 89 patients to find out why we could not detect any difference, we looked at their VA scores and the primary endpoint in this cohort of patients to see if this

cohort had a treatment benefit like the overall trial population. So, that's 275, please.

What we found looking at the primary endpoint and at the secondary endpoint, that in this cohort of patients, which is once again 89 patients, 56 and 33 considering the 2 to 1 randomization -- the primary endpoint, which is the percentage of patients who lost less than 3 lines was identical in the two groups in this particular cohort of patients. In this particular cohort of patients, the mean change in VA score from baseline was also almost identical between the two groups. So, really it was very difficult to have a reasonable interpretation of the quality of life data based on such a cohort in the trial.

DR. FONG: If there are no further questions, maybe we should talk about the draft questions for the advisory committee now. Should we move to that stage?

DR. CHAMBERS: I think we still are obligated to have at least call and see if there are any additional public -- reopen the public forum.

DR. FONG: Yes. I want to open the meeting now to the public. Are there any speakers from the public who would like to speak before the committee?

(No response.)

DR. FONG: If there are none, let's go ahead and talk about the draft questions for the advisory committee.

Number 1, how can the subgroups for which Visudyne demonstrated a visual acuity benefit be best described?

Maybe we'll start with Dr. Cioffi here.

DR. CIOFFI: I think, short of what's been discussed here as far as predominantly classic, any of the other subgroup analyses or attempts to put any other sort of qualifiers on it is probably fraught with the problems of small subgroups and we should avoid it. Taking Dr. Jampol's comment to heart about the subgroups, when we're talking about mostly classic versus not, they still remain fairly large groups which seem to be adequately powered. If we go down to other recommendations, I think we're going to get into trouble with very small numbers.

DR. FONG: Johanna?

DR. SEDDON: Well, I think it stands that the predominantly classic subfoveal choroidal neovascular membrane group would be the subgroup is targeted here as having the most beneficial effect.

DR. FONG: Leon?

DR. HERNDON: I agree that we should not break it down further than just the classic subgroup of CNV as showing a benefit from the treatment.

DR. FONG: Dr. Kilpatrick?

DR. KILPATRICK: I agree.

Dr. Goldberg -- is she going to comment?

DR. FONG: I'm sorry. Jackie Goldberg.

MS. GOLDBERG: That's okay. I think this particular question is outside my expertise. I wanted just the labeling stuff.

DR. FONG: Thank you.

DR. KILPATRICK: I agree.

DR. FONG: Well, my observations about the study is that the treatment effect is definitely there for the entire study. I think it's modest. It's not huge. However, I'm concerned about subgroup analysis. I'm not sure that I would necessarily agree on a purely academic standpoint that the subgroup analysis data is good to be relied upon. However, given that the sponsor did demonstrate an overall treatment effect, I think it's fine to narrow it down just a little bit to classic treatment because they did also show

that there was a significant treatment effect among the classic group.

Any other comments on question number 1? Wiley, is that helpful enough for you?

DR. CHAMBERS: Yes, that's fine. Thank you.

DR. FONG: Question number 2, has the safety profile/risks been adequately addressed? Let's start with Jackie.

MS. GOLDBERG: Well, this really dovetails into a labeling question. I'd like to ask the sponsor a little more specifically about the way they've got the labeling precautions set up for the photosensitivity issue. The way I understand it now, it's just in the package insert directed to whoever has got the package to look at the insert.

I was wondering if there was a mechanism where the issues of photosensitivity could be described in a handout particularly or a set of instructions directed directly to the patient so the physician would have something to give to the patient as opposed to having the physician the total control for the information. It would just be sort of a backup system.

DR. FONG: Mohammad?

MR. LANG: I'm Steve Lang. I'm with CIBA Vision.

Should verteporfin therapy be approved by the FDA, the plans that we have in place to educate the patients, the physicians, and the technicians will begin in a training program, continuing education programs that we'll be scheduling across the country. Part of that program will be on the importance of educating the patients on the concerns about being exposed to sunlight.

The tools that we'll be using: one will be a videotape that will be made available for the patients.

MS. GOLDBERG: For the patients?

MR. LANG: For the patients, yes. This will be shown to the patients during the infusion process. While they're doing the procedure, they'll be able to watch the videotape, and as part of this videotape, it will once again reinforce the importance of staying out of direct sunlight.

This will be supported by a patient brochure that once again supports the importance of staying out of direct sunlight.

Then finally, each of the patients will receive a wrist band, comparable to what you see when you check into the hospital. On the wristband will first identify the patient's

name, the date on which they were treated with verteporfin therapy, and then the warning that they should stay out of direct sunlight for the proposed period of time.

MS. GOLDBERG: Okay, thank you.

DR. CIOFFI: One question about that. Will there be a charge for those courses or is that going to be provided as free medical education?

(Laughter.)

MR. LANG: The plan right now is to have courses scheduled across the country. We're still evaluating two things: one, the financial impact of those courses. But we believe most importantly that we don't want physicians or technicians to not be educated because of particular reasons of not being able to fund attending those courses. So, the ultimate intent is to ensure that the physicians, the technicians, and even the office staff are educated on all of the benefits, features, and important events associated with Visudyne therapy.

DR. FONG: Jack, did you want to comment on question 2?

DR. CIOFFI: The safety risk. Actually one other question came to mind. Was there an exclusion on hepatic

dysfunction going into the study so that somebody that may have hepatic dysfunction and not be able to clear this drug would have to have some sort of special precaution about the photosensitivity?

DR. FONG: Dr. Strong?

DR. STRONG: The product is hepatically eliminated and, yes, there was an exclusion of moderate to severe hepatic impairment. We have conducted a study in mild hepatic dysfunction and shown no kinetic differences. So, we at this point have a warning proposed for moderate to severe hepatic dysfunction.

DR. CIOFFI: Well, then my only additional recommendation on question number 2 about the profile to risk benefits is that we may have to address someplace about hepatic dysfunction and possibly these patients need to be tested beforehand.

DR. FONG: Johanna?

DR. SEDDON: Well, related to the previous discussion, I was concerned about that as well because of the elevated SGOT, SGPT levels suggesting some effect on liver function and the elevated creatinine levels. I think until we have further data -- and it's reassuring that Dr. Jampol said

that there are not any other concerns demonstrated so far at 18 months and that some of these values did revert back to their baseline values -- I think we still need to be cautious until we have the 18- and 24-month data to actually evaluate. So, I would suggest that we indicate the warnings about hepatic function, as well as having periodic blood tests during the course of the treatment. I don't know what had been planned from the sponsor in terms of monitoring blood biochemical analyses. So, maybe we can hear from them about that.

DR. CIOFFI: Don, can I clarify? My concern was that these people with dysfunctional livers would not clear the medicine. So, my concern was about getting the medicine initially, that they wouldn't be able to clear it, and therefore would have a prolonged photosensitivity time period. I'm not concerned again about it inducing hepatic dysfunction or renal dysfunction.

DR. FONG: So, would you like to see like a relative contraindication, Dr. Cioffi?

DR. CIOFFI: Yes.

DR. SEDDON: What is the recommendation regarding monitoring these values when the patient is on the medication?

DR. CIOFFI: From my standpoint, I --

DR. SEDDON: I'm asking the sponsor.

DR. AZAB: We did follow the patients in the clinical trials with laboratory abnormalities, but I hope I've shown that most of these were normal variations for the patients, especially for the anemia and creatinine data that I have shown. There were two cases in the whole of the trial that had also mild variation of the liver function abnormalities as .8 percent related to 0 in the placebo. We don't believe that at this point in time this warrants monitoring of laboratory values during treatment specifically because also there is really no basis for an effect on the liver functions.

As Dr. Strong mentioned, the elimination is mainly biliary elimination with little metabolism. The cytochrome P450 enzymes do not play a role in the metabolism of this drug. This drug is mostly eliminated unchanged in the bile. So, as long as the patient doesn't have a biliary obstruction, there's also no problem in the elimination of the drug.

We have studied doses of the drug more than triple the recommended dose for the ocular trials, and there

were no indications of any systemic effects on the livers in the trials that studied higher doses.

So, at this point in time, we are not -- of course, for patients to be treated, they have to have normal functions or mild hepatic functions. We have data to show that there's no problem in these patients. We have indicated in the label that we did not study moderate or severe hepatic impairment for that purpose, but we are not proposing a follow-up of the laboratory values during treatment.

DR. FONG: Dr. Herndon?

DR. HERNDON: One of my main concerns was brought up earlier when we talk about the differences that the reading center and the treating center had with actually documenting what was persistent leakage. I guess this will fall under the safety profile and risk.

I would like to see not only that patients get educated and the technicians, but also the treating physicians -- I think that was mentioned earlier -- perhaps could get certified. We get certified in lasik and refractive procedures. But I think it would be nice to know that physicians who are treating actually know what a classical CNV lesion looks like. That is my main concern, that we know what

we're treating.

DR. FONG: Dr. Kilpatrick?

DR. KILPATRICK: No comment.

DR. FONG: Well, I guess I'll just restate what I said earlier, which was that I don't completely feel that the risks have been completely addressed, although it's nice to hear from Dr. Jampol that there is nothing alarming in the 18-month data. However, if we were just to look at the data today, it doesn't look like there are any glaring safety issues.

The third question is sort of a follow-up to 2. Has the safety profile/risks been adequately labeled? Dr. Seddon, let me start with you?

DR. SEDDON: Well, the labeling thus far includes the photosensitivity reaction and baseline hepatic dysfunction. Is that correct?

DR. CHAMBERS: The copy of the label that you -- you have seen both what the sponsor submitted, as well as a first cut that was made from the agency. The initial recommendation on photosensitivity was the 48-hour/2-day I believe. Was it not? Was it 1-day?

DR. FONG: 24 hours.

DR. CHAMBERS: 24 hours. I stand corrected.

My initial response to that was that it should go to 1 week.

What I've heard today from the sponsor was 3 days. Is that correct?

MR. MANDT: Yes.

DR. CHAMBERS: I am interested in comments from the committee on a time frame if they have particular comments. Either way, we'll go back and look at the particular information and the overall program that's proposed to try and warn people about that.

As for the hepatic dysfunction, yes, there are currently statements in there and we will make sure that they stay.

DR. SEDDON: I have no other comments.

DR. FONG: Leon?

DR. HERNDON: The labeling, particularly when it comes to photosensitivity, 3 days seems adequate to me based on what was presented. It seems that the two patients that had severe reactions were basically noncompliant with their physicians recommendations, as I understand it. So, 3 days is adequate from my stance.

DR. FONG: Dr. Kilpatrick?

DR. KILPATRICK: Without the background, I think because of safety it should be 1 week because of the possibility of untypical individuals who do not follow the protocol. At 1 week, what's the cost to this? The cost is that you get a lot of old people who are sitting inside watching television.

(Laughter.)

DR. CIOFFI: And hopefully seeing it.

(Laughter.)

DR. FONG: Jackie?

MS. GOLDBERG: As you're making this judgment, you should go with the most conservative estimate. Err on the side of caution on this issue.

DR. FONG: Jack?

DR. CIOFFI: No further recommendations.

DR. FONG: I agree with Dr. Kilpatrick. A week seems reasonable. It doesn't seem like there's any harm to it.

Question 4, is additional testing beyond 2 years recommended? Since we're going around the table, we'll start with Dr. Herndon.

DR. HERNDON: I certainly will like to see that 2-year data. So, I'm going to reserve judgment at this time.

DR. FONG: Dr. Kilpatrick?

DR. CHAMBERS: Dr. Fong?

DR. FONG: Yes.

DR. CHAMBERS: The question actually is beyond 2 years.

DR. FONG: Right.

DR. CHAMBERS: Do you think that the sponsor or the agency should encourage testing beyond 2 years?

DR. HERNDON: No, I don't think that's appropriate.

DR. KILPATRICK: I differ obviously in the tenor of my remarks. I think that given the time course of this condition, it is important that studies be done beyond 2 years.

DR. FONG: Jackie.

MS. GOLDBERG: No comment.

DR. FONG: Jack.

DR. CIOFFI: I believe, again as Leon said, without seeing the 2-year data, assuming it looks identical, I'm probably comfortable with typical follow-up as far as

vigilance of safety data, but I think I'm fine if it holds true.

DR. CHAMBERS: I think you can assume that all bets are off if the data does not look the same between year 1 and year 2.

(Laughter.)

DR. SEDDON: I think the 2-year data will be very important. I think there certainly should be continued evaluation, as I'm sure there will be, by the investigators and the sponsors with regard to this treatment and maybe even improving upon it in the future. But in terms of requiring that for the approval process, I would say that would depend on seeing the data at 2 years.

DR. FONG: I guess it comes to me.

I think the 2-year data is extremely important. If it doesn't confirm, obviously we'll need to reevaluate all the endpoints for the study.

I think that one of the issues that I raised before was the long-term effects of multiple treatments of this medication, and I certainly would like to see more analysis of the potential harm to the retinal vasculature and also to the retinal pigment epithelium just to see what long-

term changes are being inflicted.

As far as any additional testing beyond 2 years, I don't think that's necessary if the 2-year data is confirmatory.

Question 5, what additional clinical studies would be helpful in further evaluating the potential benefits and/or risks of Visudyne therapy? Dr. Kilpatrick?

DR. KILPATRICK: Well, thank you. This question is tied into my answer to question number 4 because maybe I interpreted the word "testing" differently from the rest of the panel. As indicated by my comments, I do not know what these studies would be, but I'm hoping that some attention will be given to improving the potential benefits and decreasing the potential risks of this therapy. I simply don't know how to advise the sponsor or anybody else to do so except in terms of my general remarks about specified, focused studies.

DR. FONG: Jackie Goldberg.

MS. GOLDBERG: I have nothing to add on this.

DR. FONG: Jack Cioffi?

DR. CIOFFI: I guess I would just suggest, as was just pointed out, that we expand the subgroups. I think

that's the obvious next step, is to expand to see who this works best in.

DR. FONG: You mean do repeat studies, stratifying for the subgroups.

DR. CIOFFI: Well, I'm not recommending repeat on the classicals, but I think that they've got some hints that in certain subgroups this may be more beneficial than others. If we could focus the therapy on those other subgroups, that would be ideal.

DR. KILPATRICK: May I ask a follow-up? Jack, do you mean that in 2 years' time an equivalent subgroup analysis might give you the information that you're looking for?

DR. CIOFFI: No, no, no. My suggestions were for some of their further breakdowns of patients where they looked at older versus younger, and the numbers became so small in a lot of those breakdowns, that we don't really have any useful information on it. I think those would be the obvious phase IV's that they should pursue.

I think, as has been pointed out multiple times, that the major subgroup analysis of the classic is good, and I think it's adequately powered and they saw a consistent change in both groups that was consistent with the overall

population.

DR. KILPATRICK: Again, my whole focus here is to try and presume that this will happen, that the sponsor and other groups will try to improve on this therapy.

DR. FONG: Johanna Seddon?

DR. SEDDON: Yes, I agree that the subgroups should be evaluated more closely and with longer follow-up time. I think the sponsor has already indicated that they have expanded their investigation to occult membranes and choroidal neovascular membranes associated with other diseases, and I think that's appropriate.

Also further evaluation of the effect of retinal vasculature and retinal pigment epithelium and so forth in ancillary studies such as that also would be important.

DR. FONG: Leon Herndon?

DR. HERNDON: I'm happy with the study design, although macular degeneration affects the great majority of the caucasian population, I think other subgroups needs to be studied. There are some studies that have shown that other groups, African Americans, have a greater rate of macular degeneration than we thought previously. So, I would like other populations to be looked at as well.

DR. FONG: The treatment effect that's been presented, as I've said earlier, is very modest, and it's not overwhelming. I'd like to see some additional studies trying to understand which patients are the ones that really get the best treatment. And I'd like to see some additional studies to look at multiple repeated treatment, whether that might lead to improvement or worsening of the visual acuity should patients be treated at 2 months instead of 3 months, more frequently, and also with the repeated treatment, whether there are additional risks. That would be real helpful.

Dr. Seddon?

DR. SEDDON: Just a comment to Dr. Herndon about macular degeneration in African Americans. Actually the early stages of macular degeneration are somewhat more common than previously presumed in terms of drusen, pigmentary irregularities, but the advanced stages of the disease, geographic atrophy and the choroidal neovascular type, which is what we're discussing today, is actually very rare. So, I think it would be very difficult to assemble a large enough sample size to adequately study this treatment in that group.

DR. FONG: We'll move on to question 6, additional recommendations and comments. I guess I'll lead

off that one.

I'd like to see the 2-year data. That's what I've said before I guess, just to confirm that there's no long-term safety and that the efficacy results are borne out, that there's no reversal of the treatment.

Additional studies. Again, to repeat myself, I think there need to be some more studies looking at the long-term effects on the retinal pigment epithelium and the retinal vasculature that's being treated.

Dr. Kilpatrick?

MS. GOLDBERG: Can we formally request that we see the 2-year data when it's in? Can that be brought back to this committee whenever we meet the next time as an add-on? I mean, we'd all like to see it.

DR. CHAMBERS: As you know, the scheduling of these meetings has been based on when we've had particular needs for things. I guess I would hope if we have that information sooner and our meeting is later, that you might want to see it sooner than waiting till the next meeting.

MS. GOLDBERG: I was looking for a mechanism to make it easy just so that we would see it. That's all I was suggesting.

DR. CHAMBERS: I'll look into what's possible.

MS. GOLDBERG: Okay, thank you.

DR. FONG: Jack Cioffi?

DR. CIOFFI: Is this for summary statements now? Is that what you're looking for?

DR. FONG: Additional recommendations and comments. I'm just reading what Wiley Chambers has presented to us.

DR. CIOFFI: This drug isn't a panacea. I don't think that it's the end all/be all. It doesn't seem like it's likely to stop loss of reading vision. It seems like there's essentially a time lag that it offers people of 6 months, maybe up to 18 months. Even in the best subgroup, the effect is modest.

On the other hand, AMD is a terrible disease. It steals vision away from a huge population, and it's a growing population. It's devastating both functionally but also emotionally to the patient, and we don't have anything right now. So, even that modest effect of a 6-month window added on to an 81-year-old's life of being able to see and function I think is significant. So, I don't want to underplay a 6-month or 18-month or 2-year window in being able to read or function

as insignificant.

With the excellent safety profile, I think this is a reasonable drug and I think we should seriously consider approving it.

DR. FONG: Dr. Seddon?

DR. SEDDON: I agree. I think the sponsor has done an excellent job of presenting the data and summarizing the safety and efficacy of this drug. There are some issues that we have discussed here I think that should be brought out in the labeling of this particular drug, with emphasis on education, on limiting the treatment at this time to the one subgroup of individuals, and then with adequate labeling and warnings. I think I would agree that at this time it should be approved.

However, I also would like to echo the other feelings of others around the table that it would be important to see the longer-term follow-up data at 2 years. But I think based on what has been presented today, I think it's reasonable to approve it.

DR. FONG: Dr. Herndon?

DR. HERNDON: I'd like to go back to the impassioned pleas of Mr. Blankenship and Mr. Thompson as they

presented their stories earlier this morning. That patient population certainly needs something. There's nothing out there at this present point, and this medication seems, at least in the early stages, to offer some benefit.

I definitely echo what Dr. Cioffi said. It's definitely worth paying further attention to this medication. We would like further data. That will be given to us I'm sure. But I think it is a step in the right direction.

DR. FONG: I agree with you, Jack, that if we had neovascular AMD, there's not a real good treatment out there. We were pushed to either doing macular translocation or subfoveal surgery. This drug looks real good.

However, as you pointed out, I think the treatment effect is very modest and it's not a panacea and it's not penicillin.

(Laughter.)

DR. FONG: Dr. Chambers?

DR. CHAMBERS: I just want to thank everyone for their comments and for spending the time in discussing the various issues.

Both now or certainly in the future, we are always interested in how best to run and have these meetings

function. If the material that you got as background was particularly helpful, was not particularly helpful, if there are ways that we can improve that for the future, please let me know, not necessarily just now but at any point. We'd like to try and make this process as easy for you since you are providing us with invaluable information.

I wish everybody a safe trip back. Thank you.

DR. FONG: Thank you.

Well, this should conclude the meeting of the Ophthalmic Drugs Subcommittee on Visudyne.

(Whereupon, at 2:40 p.m., the subcommittee was adjourned.)