DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE

Friday, August 27, 2004

8:00 a.m.

5630 Fishers Lane
Room 1056
Rockville, Maryland 20852

PARTICIPANTS

Jennifer A. Dunbar, M.D., Acting Chair
Kimberly Littleton Topper, M.S.

MEMBERS:

Paula L. Knudson
William Gates, M.D.

CONSULTANTS (VOTING):

Scott M. Steidl, M.D.
Jeffrey Lehmer, M.D.
Vernon Chinchilli, Ph.D.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH OPHTHALMIC
DEVICES PANEL MEMBER (VOTING):

Jose S. Pulido, M.D., M.S.

PATIENT REPRESENTATIVE (VOTING):

Elaine King Miller, Ph.D.

INDUSTRY REPRESENTATIVE (NON-VOTING):

Peter A. Kresel, M.B.A.

FDA STAFF:

Jonca Bull, M.D.
Wiley A. Chambers, M.D.
Jennifer D. Harris, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. DUNBAR: I would like to call the Dermatologic and Ophthalmic Drugs Advisory Committee meeting to order to review NDA 21-756, for Macugen, and I would like the committee members to introduce themselves. I am Jennifer Dunbar, from Loma Linda, California, and I would like the committee members, starting on my left, to introduce themselves.

DR. GATES: I am William Gates, from Nashville, Tennessee.

DR. LEHMER: I am Jeffrey Lehmer, from Bakersfield, California.

DR. PULIDO: Jose Pulido, Rochester, Minnesota.

DR. STEIDL: Scott Steidl. I am a retina specialist from the University of Maryland, in Baltimore.

MS. KNUDSON: Paula Knudson, with the Texas Health Science Center, in Houston.

DR. CHINCHILLI: Vern Chinchilli, Penn

State Hershey Medical Center.

DR. BULL: Good morning, Jonca Bill, Director of the Office of Drug Evaluation V, in the Office of New Drugs here, at FDA.

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

DR. HARRIS: Jennifer Harris, medical Officer, same division.

MR. KRESEL: Peter Kresel. I am the industry representative, Irvine, California.

MS. TOPPER: Kimberly Topper, FDA, the Executive Secretary for the committee.

DR. MILLER: Elaine King Miller, Amarillo, Texas.

DR. DUNBAR: Now we will ask Ms. Topper to read the conflict of interest statement.

Conflict of Interest Statement

MS. TOPPER: 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 for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of conflict of interest at this meeting with the following exceptions:

Dr. Jennifer Dunbar has been grated a waiver under 18 U.S.C. 208(b)(3) and 21 U.S.C. 505(n) for her spouse's ownership of stock of the sponsor. The stock is valued from between $25,001 and $50,000.

Dr. Jose Pulido has been grated a waiver under 21 U.S.C. 505(n) for his children's ownership of stock in the sponsor. The stock is valued from $5,001 to $25,000.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

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.

We would also like to note that Dr. Peter Kresel has been invited to participate as a non-voting industry representative. Dr. Kresel is employed by Allergan.

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

DR. DUNBAR: Now we will ask Dr. Chambers to give an introduction of the issues that we will review today.

Introduction

DR. CHAMBERS: Thank you, Dr. Dunbar. Let me start with welcoming everybody. Good morning. I want to particularly welcome the advisory committee members, and the time that they have taken both to review the material and to both

travel and attend today.

[Slide]

We are here today to discuss Macugen, and this is the Dermatology and Ophthalmology Advisory Committee meeting. Those of you who think you should be some place else, we would welcome the open seats if you want to give them up.

My name is Wiley Chambers. I am the Deputy Director for the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products, and it is our Division within the Office of Drug Evaluation V that will be reviewing this application today.

[Slide]

This application, unlike many others--or at least the section that we will be reviewing today, unlike many others, is part of the continuous marketing application Pilot 1 NDA submission which was part of PDUFA 3, which is the Prescription Drug User Fee Act that was enacted into law in 2002. This allowed for the presubmission of individual modules in different

sections that would then be reviewed, and comments given back. This would not be a final action but it would be comments on a particular section, with the goal of speeding ultimate approval of particular applications by being able to give interactive comments early on. The action on the actual NDA will only be taken after all the modules are submitted and reviewed.

[Slide]

Today's discussion is clinical only. We are only dealing with the clinical section. We are not dealing with the pharm. tox. section. We are not dealing with the chemistry manufacturing section. So, no one should expect that we will take an action on this NDA today, tomorrow or the next day because there are other modules which are being reviewed in their own time course.

The expectation is that we will give comments back to the sponsor of the application within approximately six months of the time when the module was submitted, and so we have scheduled this meeting to deal with the clinical issues and

our clinical feedback. As you will hear later on, we have particular questions that are geared toward this application, but we are looking primarily to see have we missed anything; are there other areas, while we are still within the review period, that we should be looking at further, or are there issues that you think need to be further explored before an application would be acted on one way or the other?

[Slide]

I am going to spend some time today going through basic clinical trial design issues for products for macular degeneration in general.

[Slide]

The Division gives guidance as trials are performed on a way to do a particular trial. We don't believe there is a single method to do all clinical trials. We have tried to give what we think is a good way to do trials that will give answers that we can then interpret. We clearly recognize that there may be additional ways and there may be reasons to have variance from what we

recommend. But just so that everybody is in the same page, I am going to go through what we generally recommend to sponsors of trials so you know where there are potential differences, which you may either agree with or disagree with, but more for informational purposes.

We ask that trials be parallel on design trials; randomized by person as opposed to randomized by eye; double-masked, meaning at least the investigator and the patient are masked to what treatment they are receiving; and to try to incorporate dose ranging within the study development plan. That does not mean every trial but it means that there be an exploration to dose ranging.

[Slide]

The inclusion criteria for at least wet macular degeneration, using that term as broad as that is, is that we expect patients to have choroidal neovascularization documented by fundus photography and/or angiography. We expect there to be specific observable features, including

membranes greater than a particular defined size and with particular diagnostic features such as leaking on fluorescein, such as leaking on indocyanine green or ICG, but define a particular population for which we could then label the product.

[Slide]

We try to get the trials in total to be as general as possible while still identifying a population that the product works for. Patients with concurrent ocular diseases that may be associated with choroidal neovascularization we think should be excluded to avoid any kind of confounding issues. In this particular case that generally means excluding people with presumed ocular histoplasmosis and excluding high myopia, primarily because these things can also cause choroidal neovascularization and we want to try and figure out which disease the product is working on.

[Slide]

We ask for replication. So, we want safety and efficacy, supported by at least two

independent trials of at least two years duration. We are looking for robustness in the findings. We want independent trials, and to that extent we mean geographically separate so that we know the product does not just work in Washington, D.C. or does not just work in Boston or one particular city where the water supply is unique. These trials conducted to date were each multicenter trials and so, obviously, clearly meet that criteria.

Actually, before I go on let me say one thing about the two-year trial. We have asked for trials to go on for two years and we have had discussions at this advisory committee before about how long trials should go on for. We have recognized that endpoints may be acceptable at a one-year time point but we have asked that trials continue on for two years. So, while you may not hear two-year data, you can rest assured that the trial will continue to go on for two years and we will ultimately have that information which we will factor into our decision. But we believe that, because of the age of the population, one year is a

significant portion in the rest of their lives. Consequently, if the product is showing benefit at one year we believe we could potentially approve a product and label it as working for however long it works for, but we think that duration needs to be at least one year, but have not been wedded to anything more than that. If you end up disagreeing with that, as with anything that I say today, please feel free to make those comments to us.

[Slide]

The clinical trial program we think should be able to identify adverse events that occur at least at a one percent adverse reaction rate. People may argue that one percent is too low, too high. It is, for lack of a better figure, what we have picked. That means you need at least 300 patients studied fully through that to be able to determine that. We generally recommend at least 500 patients so that we are not dealing with, "well, I've got 299" or "I've got 298" or "I've got 301." We know in this population, because of the natural age and normal life span, people are not

going to necessarily survive through the trial--just not related to the drug but related to other reasons. So, we start out asking for people to do trials of 500 patients or more.

We like the concentration to be studied that is going to be marketed, we like concentrations that are above what is going to be marketed to be studied to try and exaggerate potential adverse events so that we can get a handle of potential adverse events that may occur, even if they are not going to occur on the final product that is approved, so that we have some idea of what to look for. And, we would like the frequency of dosing to be at least as frequent as proposed for marketing. You will see in the trials we discuss today dose-ranging studies that look at different concentrations.

[Slide]

The duration, as I mentioned, should be at least 24 months but, as I also said, the endpoint could be as short as 12 months.

[Slide]

We do not require multicenter trials. It is certainly easier to enroll larger number of patients with multicenter trials. Our preference, if a company is going to do a multicenter trial, is that there be at least 10 patients per arm per center. We have set that number so that we can look at investigator interaction. Now, that is frequently a difficult thing, to enroll that many patients per arm per center, particularly if you have a multi-arm study and you are doing dose ranging. That dramatically increases the number of patients you would have at a particular center.

You need to recognize that if we do not have that many we are probably not going to be able to look for investigator interaction at any one particular center. We will do some other things to look at that question but to get a true, you know, is there one investigator that is disproportionate to other investigators really requires more patients than you will see in these particular trials. This is not an uncommon problem that we have. We don't have a solution. Generally, if you

are able to enroll a large number of patients at any one center you probably wouldn't do a multicenter trial. So, again, we welcome suggestions on how to get around this.

[Slide]

Stratification is not necessary. If there is a chance of imbalance in factors that someone believes may influence the results, and in this case there have been discussions about whether occult versus classic potentially would influence the results or whether baseline visual acuity would potentially influence the results. We have suggested that people stratify so that they have a higher chance of having an equal distribution between the individual groups--again, not required. The hope is that randomization will take care of it but stratification frequently helps.

[Slide]

Control agent--we have asked that at least one of the clinical trials that is performed demonstrates superiority to a control. We have not defined what that control has to be. It could be

the vehicle; it could be a sham; it could be a lower dose; it could be a different product. By saying at least one trial has to demonstrate superiority, that means we also potentially would accept an equivalence trial. In today's discussion we are going to deal primarily with superiority trials but, recognize, we potentially would accept either a superiority trial or an equivalence trial.

We prefer a vehicle control given our druthers of different choices, and we prefer that because it minimizes the bias. There is some animal evidence--we are not aware of any human evidence to date but there is some animal evidence that mechanical manipulation may initiate inflammatory mediators that may help the condition. Consequently, by not having something that simulates that same pathway, there may be some influence going on by the way you deliver the product, in this case the intravitreal injection, that may be a positive effect. But there are ethical issues, and I am sure we will probably get into some of that, with giving vehicle controls.

One of the most common reasons cited for not giving a vehicle control is the risk of endophthalmitis. We recognize that there is a theoretical risk of getting endophthalmitis in the vehicle group. The clinical trials that were performed here had cases of endophthalmitis that were in the active control group.

I just want to be on record for stating that, to the agency's knowledge, we have not had a case of endophthalmitis in the vehicle control group in any trial that has run that, and there have been trials that have run it. So, we continue to think it is not unethical to run a vehicle control. Should we get an endophthalmitis case, which I am not hoping for anyone, we may change that opinion but at the present time we continue to recommend vehicle controlled trials.

We do reluctantly accept sham controls, but we have put a condition any time we have accepted sham controls, and that has been that we have wanted additional doses, in other words, more than one dose tested to try to aid in the masking

of the trial. You will see that in the case of these trials today there are multiple doses, in addition to the sham, that is conducted. Again, we recognize that having a sham increases the chance of bias influence in the results, although just having a sham does not necessarily create bias.

[Slide]

Dose ranging--we prefer to try and bracket the dose that will ultimately be marketed, in other words, study doses that are higher and study doses that are lower than that which will be ultimately marketed so we get a better understanding of the drug product.

[Slide]

Efficacy has been discussed a lot. We have a number of parameters that we readily accept as being acceptable. We have other parameters which we think may in the future be acceptable or we will be willing to entertain if there is validation, and validation does not necessarily need to occur in this particular trial. The thing that we readily accept as being important is a

change in visual function. So, our guidance to people when we are having discussions about clinical trials is that there be statistical significance in clinical relevance in visual function at more than one time point. By visual function we mean visual acuity, visual fields or color vision.

[Slide]

The evaluations we expect to be carried out include, obviously, best corrected distance visual acuity. By that, we generally mean using a chart that has equal number of letters per line and equal spacing between lines. The ETDRS is one type of chart that meets that, and based on the validation information that was conducted at a four meter distance so that is our preferred both distance and test but we are willing to recognize other equivalent tests of best corrected distance visual acuity.

We expect best corrected visual acuity to be measured at every visit, and we expect those visits to occur no less frequently than every three

months.

We expect to have dilated seven field fundus photography sometime during the trial. We expect to have fluorescein or indocyanine green depending on what exactly is being studied during the trial, and we have not specified exactly when that has to be. We expect dilated ophthalmoscopy to be performed both for evaluation and for safety at every visit. We expect a dilated slit lamp exam for the same reason. We expect to have endothelial cell counts, not necessarily in every trial but somewhere within the development plan, and have at least one study that includes it at the beginning and end of the trial, and the same thing standard systemic clinical and laboratory evaluations.

[Slide]

Two meters versus four meters has been a source of a lot of controversy. It is my understanding it stems primarily from the practicality of being able to have exam rooms that are four meters. In my father's day and age, it would have required 20 foot length and his exam

rooms were set up to do that. That is not the current trend now. People use exam lanes that are much shorter. But the subject has been studied. It was the source of a lot of discussion in the past, and there is a paper that set out four meters as a standard that was published in Ophthalmology in 1996 for exactly the purpose of discussing what the best distance is.

It does not mean that you can't theoretically correct. You know, two meters, four meters--you can use the same distance and make the charts smaller so you are looking at the same angle that gets subtended. The issue is the variability that occurs when measuring at two meters versus four meters and the potential for any bias if the patient is allowed to lean. Now, if we would strap down or lock every patient into an exam seat and never let them move at all, it probably wouldn't be an issue but we don't do that. Just so people get a feel, at a two meter distance 17 inches is equal to one of one line. Those of you sitting in the various seats, if you are leaning backward or

leaning forward, just sitting in your same seat can easily do 17 inches. We don't have any reason to believe that people are attempting to bias the results or attempting to lean, and visual acuity is a very common measure in ophthalmology so everybody is aware to try to keep people from leaning or keep that from influencing what goes on. But studies have been done that show poor reliability at one meter versus four meters. So, the assumption is that there is also more variability at two meters than there would be at four meters. The overall impact on a particular trial is not known, and the only way to know that for sure would be to do both two meters and four meters, which we do not have data to discuss today.

We think it is more significant for those trials that have a feature that allows there to be a potential in masking, such as sham. We think it is more of an issue in an equivalence trial than it is in a superiority trial. These trials that we are talking of today are superiority trials; they are not equivalence trials. But there are issues.

[Slide]

Our recommended endpoints to date have all been, as I mentioned earlier, visual function. We think at some point in the future we will end up accepting anatomical changes but we have not yet found anatomical changes that correlate directly with visual function. So, currently we readily accept doubling of the visual angle, which on the ETDRS chart at four meters would be 15 letters or more; a halving of the visual angle, in other words, showing improvement in vision; a quadrupling of the visual angle, which would be 30 letters or more. These are all looking at percentage of patients that have this particular finding because we think a doubling of the visual angle is a clinically significant difference that would not occur within the variation of day-to-day visits.

[Slide]

We have also been willing to accept a difference in the group mean. We do not know exactly how much of a difference in group mean would be clinically significant so for

consistency's sake we have said we will readily accept a mean change of 15 letters. That does not mean that something less than that may not be statistically significant. We are just not ready to accept without question anything less than 15 letters.

[Slide]

Let me just briefly talk about equivalence trials just so you know the full scope of what we have talked about with individual sponsors. We believe it is possible to do comparison with an active agent which has already demonstrated repeated success. Visudyne is currently approved for predominantly classic choroidal neovascularization in atrial macular degeneration and a couple of other things. So, for that particular indication we would accept an equivalence trials if one wanted to conduct it. The way we have set up equivalence trials is that we have asked that at least 50 percent of the established treatment effect be preserved so that 95 percent confidence intervals be drawn around

those parameters to protect at least 50 percent of the treatment effect. Again, it is not a particular issue for this product but it may be an issue for other products.

The analyses that we ask to be conducted always include intent-to-treat with last observation carried forward and per-protocol with observed values only. We recognize these as differences in the data available for analysis. The intent-to-treat last observation carried forward is the fullest data set we can obtain. It is everybody that was randomized in the trial and it is creating a value for everyone whether real of extrapolated. A per-protocol analysis is the minimal data set. It is only those patients that fully met the protocol and only the values that we have there.

We don't believe that either one of these two analyses is the best analysis or is the most proper or is the most representative. We think they are extremes and we ask that both be conducted and we look for differences between these two

analyses. If there are no differences between these analyses we assume that, regardless of how much inclusion/exclusion, your results are pretty much the same and you can accept either one. If there are differences we ask for additional analyses to try and explore which one is likely to be telling a better picture or why it is telling a different picture.

Other analyses which you would have seen in the briefing package include things like worst-case analyses where we treat all dropouts in the control as being successes and all dropouts in the test product as being failures. This is not a correct test. This is not an accurate test. We are making assumptions in the worst direction to look and see how robust the findings are. We don't expect the product to win on a worst-case analysis, but it does give us an idea of what the limits of potential analysis results could be.

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As a general rule, we ask for alphas to be 0.05. This is the common 5 percent for two-tailed.

In other words, p is less than 0.5. We ask for power to detect a difference to be 80 percent or greater, and we ask that any time anybody looks at the data, any kind of look any time during the evaluation that there be an adjustment in the statistical plan, in other words, correction for that alpha for any look that occurs. All of our analyses that you see in any of our data sets will include these features.

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The last one I want to talk about is pediatrics. There is an agency initiative to try and include, when possible, pediatric patients in the drug development of particular products. So, I am covering it for completeness. In this particular case, choroidal neovascularization is rarely seen in pediatric populations and we have not asked the sponsor of this application or any of the applications that just deal with choroidal neovascularization to include pediatric patients because the population we don't think is relevant in this particular case. But as a general rule we

do ask for pediatric patients to be included during the development.

I am happy to take any questions and, again, I thank everybody for your time, and look forward to a fruitful discussion.

DR. DUNBAR: Are there any questions at this point regarding Dr. Chambers' presentation? If not, at this point then I would like to open the forum for the sponsor, Eyetech Pharmaceuticals and I will ask that the sponsor introduce each of their speakers within their presentation.

Eyetech Pharmaceuticals Presentation

Introduction

DR. DYER: Good morning.

[Slide]

Today we will discuss the first anti-VEGF therapy for the eye and the first treatment to target the underlying biology of neovascular age-related macular degeneration. Pegaptanib sodium achieved statistical significance for clinically meaningful, prespecified primary endpoint in replicate trials with strong supportive

data in secondary endpoints.

The efficacy was against usual care controls, and this pharmacological agent also shows a favorable safety profile and provides a treatment benefit to many patients for whom no effective therapy presently exists.

[Slide]

My name is David Guyer. I am from Eyetech Pharmaceuticals. I previously was professor and chairman of ophthalmology at the N.Y. School of Medicine and a practicing ophthalmologist specializing in macular degeneration.

Also speaking today will be Dr. Tony Adamis, who was an ophthalmologist on the full-time faculty at Harvard, and is now with Eyetech. He ran the ocular angiogenesis laboratory as well. Our risk/benefit section will be presented by Prof. Don D'Amico, from Mass. Eye and Ear Infirmary at Harvard.

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Neovascular age-related macular degeneration represents 90 percent of the severe

vision loss from this disease. Many patients note a loss of independence and inability to read, to ambulate and to recognize faces of their loved ones. This occurs because when the disease forms abnormal blood vessels that leak blood and fluid waviness or blurred vision can be seen in the central area that sometimes can lead to a scotoma or blind area centrally that prevents them from seeing straight ahead, and in up to a third of patients clinical depression can be noted.

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The devastating effects of this disease were well summarized in a book by Henry Grunwald, who was the former editor-in-chief of Time Magazine and U.S. ambassador. In the book, "Twilight: Losing Sight, Gaining Insight" Mr. Grunwald said, "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."

[Slide]

Macular degeneration represents a major

public health problem and urgent unmet medical need. It is the most common cause of irreversible, severe blindness in developed countries. Ninety-five percent of retinal specialists believe that macular degeneration represents an epidemic, and there are 200,000 new cases a year in the United States alone, and a prevalence of up to 1.6 million patients with active bleeding. Limited treatments are available and 85 percent of retinal specialists are dissatisfied with current treatment options.

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Macular degeneration represents a progressive disease. Early on in the disease these whitish-yellow spots, called drusen, occur and patients can progress to the neovascular form of the disease which is where pegaptanib is effective. This is an angiogenic disorder and what happens is abnormal blood vessels grow behind the retina where they leak blood and fluid, as depicted here, and, untreated, they lead to disciform scarring where fibrovascular tissue destroys and replaces the

normal rods and cones in the retina. At this point, usually moderate to severe visual loss is noted.

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Let's discuss the therapeutic options available for patients with neovascular macular degeneration. In the 1980s, the Macular Photocoagulation Study Group showed the beneficial roles of thermal laser photocoagulation. However, very few patients are suitable for this treatment. The treatment is most suitable when the abnormal blood vessel, as seen here on a fluorescein angiogram, is away from the center of the macula, in what we call extrafoveal or juxtafoveal location, because for patients where the blood vessel is dead center or subfoveal the laser scar itself can destroy the very tissue we are trying to save. Unfortunately, most patients with neovascular macular degeneration have subfoveal disease where the blood vessel is dead center.

[Slide]

In the year 2000, photodynamic therapy, or

PDT, was FDA approved for patients with subfoveal predominantly classic angiographic subtype. Thus, for approximately three-quarters of patients with neovascular macular degeneration there is no FDA approved therapy, although there is off-label use, with some limited CMS reimbursement, presently.

Today we will discuss the first anti-VEGF therapy for the eye, a pharmacological treatment that targets the protein VEGF that is responsible for the hallmarks of all choroidal neovascularization. Increased levels of VEGF lead to neovascularization and increased permeability, which lead to the clinical features of all choroidal neovascularization, and pegaptanib blocks VEGF.

[Slide]

VEGF is the common denominator for neovascular macular degeneration. Numerous peer reviewed papers have shown that for all angiographic subtypes, by immunohistochemistry staining, VEGF is present in both autopsy and surgical specimens.

[Slide]

Pegaptanib sodium is a pegylated modified oligonucleotide. It has a selective vascular endothelial growth factor antagonist to isoform 165. Tony in just a few minutes. It is a sterile aqueous solution in a single-use, pre-filled syringe, which is important for safety reasons. The recommended dose is 0.3 mg of intravitreous injection administered once every 6 weeks.

[Slide]

We will show you today that pegaptanib met a clinically meaningful primary efficacy endpoint with statistical significance in replicate, well-controlled clinical trials, with a favorable safety profile.

[Slide]

I will now ask Tony Adamis to discuss a VEGF overview and macular degeneration pathophysiology.

VEGF Overview and Macular Degeneration Pathophysiology

DR. ADAMIS: Thank you, David and good

morning.

[Slide]

In 1971 Judah Folkman first proposed the targeting of a specific angiogenic factor as a way to treat disease, and specifically a way to treat cancer and ophthalmic disease.

[Slide]

It was in 2004, with the completion of pivotal Phase III trials using Avastin which blocks VEGF that this theory was in a definitive fashion proven correct. This drug now was approved this year as a first-line therapy for colon cancer. So, we entered this era of biological anti-angiogenesis therapy.

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The target in that trial and in our trial is VEGF, which is an acronym for vascular endothelial growth factor. Prior to that it was called vascular permeability factor. Unlike many other growth factor names, these two are very appropriate in the sense that they describe the central biological functions of this protein. VEGF

makes vessels very leaky and VEGF makes vessels grow. The leaky aspect of it was discovered in 1983 by Harold Dvorak and then the neovascularization aspect or biology of VEGF was discovered by Napoleon Ferrara, who has been a leader in this area, and Dan Connolly, in 1989.

Since then, if one conducts a MEDLINE search, there have been over 11,000 published peer reviewed articles on VEGF. There is a large body of knowledge concerning this growth factor. I show you just one example of that here. This is the protein structure of VEGF. We now can determine very precise structure-functional relationships.

[Slide]

The disease we are here to discuss, as David said, is age-related macular degeneration, a very prevalent disease in our society and a very complex one scientifically when one begins to study it. We are beginning to unravel the earlier stages of the disease, the stages where Bruch's membrane is altered and gives you those yellow spots, the drusen that David showed you in a clinical

photograph. We are also starting to understand the complex interaction of the different cell layers with the vasculature. But the area or the phase of the disease, the late phase of the disease that we are studying is the neovascular phase where vessels begin to grow up towards the retina. These vessels are abnormal and leaky, and they leak fluid and lipid and they damage the photoreceptors which sense light, and people lose vision and go blind. This process, the angiogenic process, has been very well studied.

[Slide]

As David said, the data indicate that it is biologically plausible that blocking VEGF would have a beneficial effect in this disease in a broad population. When one looks at surgical specimens or autopsy specimens of patients with the disease, what is seen is that the common denominator is VEGF. It is present in all angiographic subtypes and it is present in all active stages of the disease. So, therefore, the hypothesis that blocking VEGF in neovascular MD would have a

broad-base effect has some broad biological plausibility.

[Slide]

But those are not the only data that we have. There is a large body of preclinical evidence, roughly 15 years worth, which is summarized on one slide here. Let me just briefly walk you through it. In preclinical models of vessel growth in the cornea, in the iris, in the retina and in the choroid, if one gives a VEGF inhibitor you can prevent the growth of vessels and you can prevent the leak that is associated with those vessels. So, VEGF seems to be required for those processes.

Similarly, if one looks at those normal tissues and now introduces VEGF into the system, either by injecting the protein or genetically over-expressing it, VEGF in and of itself is sufficient to produce the neovascularization or leak that can occur in these tissues.

Then, so that we have some context in which to interpret those preclinical data, surgical

specimens and autopsy specimens from humans with actual corneal neovascularization, iris neovascularization, retinal and choroidal neovascularization show that VEGF is expressed at high levels in those tissues at the time when the vessels are growing and leaking. So, the totality of the data supports this approach of blocking VEGF in specifically the disease under study today, age-related macular degeneration.

[Slide]

It gets a little more complicated in the sense that VEGF really refers to a family of related molecules, and I want to talk about one specifically, VEGF 165 which is the target of pegaptanib.

[Slide]

We were faced with the paradox a few years ago, as we looked at the accumulated data concerning the role of VEGF in disease and in the normal state. What we found was that VEGF is required for the normal formation development of vessels during development throughout the body. I

am just showing you here two examples. These are the vessels of the normal colon and these, obviously, are the normal vessels of the retina.

[Slide]

In the same molecule, VEGF was shown in a number of definitive studies and laboratories around the world that VEGF is required for the abnormal vessels that can grow in the colon, and this is colon carcinoma, and here is a case of age-related macular degeneration. So, how is it that the same protein can cause these vastly different phenotypes, these different types of vessels? One set of vessels are normal and they don't leak and they behave appropriately; another set looked very different and they behave very differently.

[Slide]

Perhaps, we thought, some of that complexity is encoded in these different isoforms. Let me just explain what those are. There is one VEGF gene but that gene encodes multiple transcripts or mRNAs for VEGF that have different

sizes that translate into different proteins. So, one of those major proteins or isoforms is VEGF 165, which just simply means that it is composed of 165 amino acids. Another major isoform, especially in the eye, is VEGF 121. We asked the question could it be that differential expression or synthesis of these isoforms underlies the complexity that we see in the vessels in the normal and the diseased state?

[Slide]

So, in an experiment we conducted and published last year, we studied the retinal vessels. We studied the normal retinal vessels that are developing as the retina forms and we studied abnormal retinal vessels in a model of retinopathy prematurity. This is a model where vessels grow towards the vitreous and leak and are distinctly abnormal.

What we saw was that when normal vessels are developing the isoform expression of the two major isoforms, 120 and 164 which are the rodent counterparts to human 121 and 165, is roughly equal

during development. But rather strikingly, during disease when disease vessels are growing there is a shift to almost exclusive expression of the 164 isoform. So, it was an interesting association that we saw of 164 with diseased vessels.

[Slide]

But to really get at the causality of 164 in the production of diseased vessels we conducted the following experiment. In a model of abnormal vessel growth we gave pegaptanib which blocks just 164 and compared it to a non-selective VEGF inhibitor which blocks all the isoforms. We saw that bpth were equally effective in preventing abnormal vessel growth. Here is the control with the abnormal vessels, and both are pretty good at inhibiting that.

We also looked in a model of normal retinal vessel development and, again, gave pegaptanib and what we saw was essentially zero inhibition of normal vessels. We did not affect normal vessels. Whereas, the non-selective VEGF inhibitor had a deleterious effect on these normal

vessels in the retina. So, the conclusion we made was that VEGF 164 may be preferentially associated with disease and targeting it gives you a much more selective inhibition in that you are much less likely to affect normal vessels in the developing animal. But I will tell you that there has subsequently been independent support of this, specifically from UCSF, where this is also perhaps true in the adult animal.

[Slide]

To be certain of our conclusion because we used a reagent here, pegaptanib in particular, we wanted to make sure this conclusion was robust. So, we created animals genetically that where we deleted specifically the 164 isoform and these animals were able to make all the other types of VEGFs. What we see here is that these animals have completely normal retinas and normal retinal vessels and they are no different than animals that make all VEGF isoforms. In fact, these animals grow up to a normal age. They can reproduce. There are no abnormalities we can detect, even

though they cannot make any VEGF 164.

[Slide]

So, how was a drug made that specifically blocked VEGF 164? Well, pegaptanib is an oligonucleotide aptamer. It specifically is 28 nucleotide in life. Aptamers are molecules that will fold in a very specific fashion. They have a three-dimensional conformation such that they will bind to the target protein of interest--in this case it is VEGF--in a highly specific manner, and in the case of pegaptanib with a very high affinity. This binding occurs extracellularly. The drug does not enter the cell. It is all happening outside the cell, which is where VEGF is residing. These features make it act very much like an antibody but there are some important distinctions, aside from it not being an antibody; it is an oligonucleotide.

This class of molecules, in the published literature and it has been our experience as well, are quite non-immunogenic. In our preclinical and in our clinical examination of pegaptanib we have

not seen a single instance when an antibody is raised to it. And, as I alluded to, they have this remarkable target specificity and this simply attests to that.

[Slide]

This shows that pegaptanib is very efficiently binding to human VEGF 165 and murine or mouse VEGF 164, but there is no significant, or essentially no binding to VEGF 121 or related family member of placental growth factor.

[Slide]

So, what we would expect when pegaptanib is administered to the eye is that you would have selective VEGF inhibition of 165 which was associated with pathology and in our animal model spares the normal vasculature, and we would have two very important biological responses as a function of that blockade: vessel growth would be inhibited, as would permeability, and the thinking was this would translate to a better visual outcome.

[Slide]

The last thing I would like to talk about is how we chose our dose. This drug is administered to the eye nine times a year, and there are three doses that we chose.

[Slide]

Let me show you the data that we had in hand when we were planning these trials. We knew from our pharmacokinetic experiments that when pegaptanib is given to the eye via intravitreous injection it slowly exits the eye and it can be measured in the plasma. Actually, the plasma levels mirror the levels that one sees in the vitreous. So, by sampling the blood you can infer what is happening in the eye.

The other important thing that we learned here is that when the drug exits the eye, at least in this rabbit model, you have thousand-fold less concentration in the plasma than you do in the eye. In a more relevant primate model we saw that this held up in the sense that it was 800 times less in the plasma than it was in the eye.

[Slide]

We learned from those studies that the half-life in the primate vitreous is approximately four days. We also had data that we had collected in tumor models and in a model of retinopathy prematurity that when you give pegaptanib intravenously the amount of pegaptanib that is needed to inhibit the VEGF is about 1 ng/mL.

We also had another inhibitory concentration that we had determined in vitro in tissue culture in various assays of calcium mobilization and endothelial cell proliferation. The relevant concentration in tissue culture of pegaptanib that was required to inhibit VEGF was significantly lower. It was 0.01 mcg/mL or 10 ng/mL.

When we started out it was not entirely clear which of these inhibitory concentrations would be most relevant when you are injecting the drug into the eye. So, we postulated that if this is the most relevant inhibitory concentration, then a 3 mg dose, given every 6 weeks would sufficient block VEGF for the entire 6-week period. If, on

the other hand, this was the relevant concentration, the 3 mg dose, the 1 mg dose and the 0.3 mg dose would actually all three be sufficient to block VEGF for the entire 6-week period, and perhaps that may translate to a plateau of the dose response.

[Slide]

To summarize what I have just discussed, VEGF appears to be an important control point for neovascularization and vascular permeability, the pathologies that lead to vision loss in age-related macular degeneration. Pegaptanib specifically targets the VEGF isoform VEGF 165, which we believe is operative in disease. I have shown you data from ROP but this has also been shown to be true in choroidal neovascularization, diabetic retinopathy and other conditions. And, pegaptanib dosing is based on pharmacokinetic data which were collected prior to the conduct of this study.

[Slide]

At this point, Dr. David Guyer will return and David will talk to you about our clinical

efficacy data from the pivotal trials.

Pegaptanib Clinical Efficacy

[Slide]

DR. GUYER: In this section we will show you that pegaptanib met a clinically meaningful primary efficacy endpoint with statistical significance in independent, well-controlled, replicate trials, with a favorable safety profile.

[Slide]

The macular degeneration program consisted of 6 trials, 1,281 patients and over 10,000 treatments at 117 sites in 21 countries. The dose ranges that were studied ranged from 0.25 mg to 3 mg per eye.

[Slide]

These are the six trials. EOP1003 and 1004 are pivotal trials, sham-controlled, double-masked, randomized trials. There were 622 patients in the predominantly ex-U.S. trial and 586 in trial 1004 in North America. The other four, smaller trials were pharmacokinetic trials and open-label single or multiple dosing trials with,

or without PDT, for the total exposed of 1,281.

[Slide]

The Phase I/II program showed that pegaptanib appeared safe in all tested doses and regimens with no dose-limiting toxicities. There were no unexpected retinal or choroidal abnormalities noted by angiography as read by an independent reading center. As Tony mentioned, these trials established the dosing regimen based on pharmacokinetics.

[Slide]

The study objective of the pivotal trials was to establish a safe and efficacious dose of intravitreous pegaptanib sodium in patients with subfoveal choroidal neovascularization secondary to age-related disease.

[Slide]

The development of these pivotal studies was done in conjunction with our expert advisory panel, whose names are listed on this slide.

[Slide]

The study design was two randomization,

double-masked, sham-controlled, dose-ranging trials of pegaptanib 0.3 mg, 1 mg and 3 mg and sham. The treatment regimen was every 6 weeks and the prespecified time point for the primary endpoint was 54 weeks. PDT, photodynamic therapy, was permitted per the FDA-approved label at the masked investigator's discretion. Since shams could have PDT, this represented a usual care control group.

[Slide]

Independent monitoring was done both by an independent reading center that confirmed the eligibility prior to randomization, and an independent data safety monitoring committee, or IDMC.

[Slide]

These were the members of the IDMC. It was chaired by Prof. Alan Bird, who is here with us today.

[Slide]

Because of the biology of neovascular macular degeneration and the mechanism of action of pegaptanib, we designed a trial with a very wide

range of inclusion criteria which included a broad range of visual acuities, 20/40 to 20/320, and broad angiographic criteria including all subfoveal angiographic subtypes; lesion sizes up to and including 12 total disc areas in size; greater than or equal to 50 percent of the total lesion size needed to be active choroidal neovascularization; and for minimally classic and occult disease subretinal hemorrhage and/or lipid and/or recent change in vision was necessary for inclusion.

[Slide]

Ocular exclusion criteria included previous subfoveal thermal laser therapy, and to avoid older chronic cases any subfoveal scarring or atrophy or greater than or equal to 25 percent of the lesion being scarred or atrophic. Causes of choroidal neovascularization other than age-related diseases were excluded, and if a patient had recent intraocular surgery or was thought to perhaps need cataract surgery in the near future, they also were excluded. Finally, no more than one prior PDT treatment was allowed.

[Slide]

The general exclusion criteria included a history or evidence of severe cardiac disease such as myocardial infarction within the last 6 months, ventricular tachyrhythmia or unstable angina; evidence of peripheral vascular disease; or clinically significant hepatic or renal dysfunction; or a stroke within the last 12 months. Our population, however, was very characteristic of your typical elderly population in that 50 percent of the patients had systemic hypertension; 25 percent were on statins; and 20 percent had cardiovascular disease.

[Slide]

Stratification at randomization included study center, a history of prior PDT use and angiographic subtype.

[Slide]

Our primary efficacy endpoint, which was prespecified, was the percent of patients losing less than 15 letters from baseline to week 54, the same endpoint that was used for marketing approval

of Visudyne.

This is an ETDRS chart where 5 letters equal 1 line, and the 15-letter change or 3-line change represents a doubling of the visual angle which is a clinically meaningful change to an individual patient.

[Slide]

Our primary endpoint used in intent-to-treat, or ITT, population included patients receiving at least one treatment and a baseline visual acuity measurement. The last observation carried forward, or LOCF, was used to impute missing data. We will also discuss supportive visual and angiographic endpoints, as well as exploratory or subgroup analyses.

[Slide]

This table shows the various study visits. Of note, a telephone safety check was done 3 days after treatment. Tonometry or measurement of intraocular pressure was done both before treatment and 30 minutes after, and fundus photography and fluorescein angiography was done at baseline and

weeks 30 and 54.

[Slide]

In order to preserve the integrity of the masking there were two physicians involved in the trial. One physician administered the study treatment and the second physician was involved in any patient assessments or decisions. Patients were also masked in that the sham procedure was identical to the active drug procedure except for the actual penetration into the vitreous. This meant that they had application of a lid speculum, instillation of topical medications, subconjunctival anesthetic, and pressure against the globe using a needle-less syringe.

The visual acuity examiners were also masked to both he treatment arm and also to previous vision assessments, and the reading center was not aware of the patient's treatment arm.

[Slide]

This slide represents the patient baseline characteristics for both trials 1004 and 1003. What we can see in each trial is that the active

doses and the sham are well balanced with respect to sex, age, initial visual acuity, angiographic subtype, prior use of PDT and lesion size. The only difference between the two trials was that there was slightly more prior PDT use in trial 1004. That was the North American trial, and that was because Visudyne was approved and reimbursed earlier in the United States than in Europe. Out of 9 possible injections, on average all patients, treated and sham, received 8.5 of the 9 injections, and overall there was about a 10 percent rate of discontinuation in the trial.

[Slide]

We prespecified to use a Hochberg procedure to account for the multiple doses in this pivotal trial. As per agreement with the FDA, it was decided to unmask study 1004 first--that was the trial that was recruited first, thus, the results were available earlier--in order to determine which doses to formally analyze in the study trial study, 1003.

[Slide]

So, we proceeded to unmask the first trial, study 1004, and we found for the 0.3 mg dose 67 percent of patients lost less than 15 letters compared to 52 percent of sham. This hit our Hochberg adjusted p value at 0.0031. Note that the 1 mg dose had a similar response rate, about 66 percent. The p value was 0.0273. The 3 mg response rate was higher than the shams at 61 percent, however, it did not hit the necessary p value.

[Slide]

For this reason, prior to unmasking the second trial, it was prespecified to the FDA that only the 0.3 mg and 1 mg doses would be formally analyzed in the second trial. Then we proceeded to unmask the second trial, study 1003.

[Slide]

This study showed replication of the findings of the first trial study, 1004, in that 73 percent of the patients in the 0.3 mg dose, compared to 59 percent of sham, lost less than 15 letters, again hitting our Hochberg adjusted p

value of 0.0105. Again, the response rate in the 1 mg group was similar at 75 percent and a p value of 0.0035, and the response rate in the 3 mg group was 69 percent. The p value you see here, 0.1252 was a nominal p value because we decided, as we mentioned, not to formally analyze it.

[Slide]

So, we can look at the combined data and see that 70 percent of the 0.3 mg group, 71 percent of the 1 mg group and 65 percent of the 3 mg group lost less than 15 letters compared to 55 percent of the shams, and for all of these active treatment groups we had low nominal p values.

It is important to emphasize that for the 0.3 mg group we were able to show independent replication in two trials of a statistically significant effect in a prespecified clinically significant primary endpoint.

[Slide]

I would like to turn now to some supportive visual angiographic analyses. There are a variety of ways of looking at various visual

outcomes that are standard for reassurance that the treatment effect for showing the primary endpoint is real. As we will present, all of these analyses were in favor of pegaptanib which gives us confidence in this treatment effect. Because the independent trials had the same protocol and demographics, and because we prespecified it in our statistical plan, we will present these as pooled data.

[Slide]

This graph shows the percent responders over time. What we can see is that we were able to show that the active treatment group had a treatment effect over sham not only at our primary endpoint at 54 weeks, but at every studied time point the active treatment group did better than the sham.

[Slide]

This is a graph of mean change in visual acuity. Again, the active treatment group is here, the sham or usual care group showing a progressive decrease in vision, and the difference at 54 weeks

was approximately 50 percent in favor of the active treatment group.

[Slide]

This treatment effect was early and sustained, by as early as 6 weeks, which was the first visit after the first injection the pegaptanib groups had already distinguished themselves from the controls and, as we can see here, the 0.3 mg and the 1 mg group had done that with the low nominal p value. This sustained itself throughout the 54-week course of treatment.

[Slide]

Sham eyes were twice as likely to suffer severe vision loss than actively treated patients, as shown in this graph of percent of patients with severe vision loss. We can see the sham controls with severe vision loss compared to the active-treated groups.

[Slide]

At week 54, again, there was a low nominal p value for the 0.3 mg and 1 mg group compared to sham, with progression to severe vision loss which

is 30 letters or 6 lines.

[Slide]

This also was seen for legal blindness in one eye, which is 20/200 or worse. We again can see that more sham eyes progressed to 20/200 vision or worse compared to actively-treated groups.

[Slide]

Patients on pegaptanib were also more likely to maintain and/or gain visual acuity. This graph shows the prespecified endpoints of maintaining or gaining vision that is greater than or equal to zero lines gained, as well as greater than or equal to 3 lines gained. These other two endpoints were not prespecified but we can see again in all cases a treatment effect for maintaining or gaining vision compared to sham.

[Slide]

The next few slides will show the distribution of visual acuity change at baseline and compared to week 54. Let's first look for the 0.3 mg group. This was the range of visual acuities at baseline. Yellow is the 0.3 mg group

and blue is the sham.

[Slide]

After 54 weeks in the trial we can see that more patients in the 0.3 mg treated group than sham had good visual acuities and more patients with sham than treated patients had poorer visual acuity. So, the shift in distribution was in favor of our 0.3 mg group, and the p value for this was less than 0.0001.

[Slide]

The same is true, as we can see here, for the 1 mg group. This is the baseline visual acuity distribution and at 54 weeks again we can see more 1 mg treated patients than sham having relatively good visual acuities and more shams than treated eyes having poorer vision. Again, this shift in distribution is in favor of the 1 mg group had a p value of less than 0.0001.

[Slide]

Finally, we can see that for the 3 mg group also. Here is the baseline distribution and at 54 weeks again more 3 mg patients had better

visual acuities than shams, and more shams had poorer vision at the end of 54 weeks than the 3 mg treated patients.

[Slide]

This is a graph of the cumulative distribution function of vision. What it shows on the bottom is the change in visual acuity up to week 54 and the cumulative proportion on this axis. This shows the robustness of the data as it uses all of the data points for 54 weeks.

What we can see first is this S-shaped curve. This is the blue sham patients. You can see here, for example, at minus 15--that is minus 15 letters which was our primary endpoint, moderate for vision loss, and we see minus 30 which, as we talked about, represents severe vision loss, and we can see the zero or higher time point which represented maintaining vision. What we can see is that, whether we are talking about preventing vision, maintaining vision or gaining vision, there has been a shift in distribution, a shift in the distribution of the sham patients in all active

treatment arms to the right, suggesting benefit in all areas. The area between the lines which represents this improvement was highly statistically significant for all three doses, for the 0.3 mg dose less than 0.0001; the 1 mg dose 0.0001 again; and the 3 mg dose 0.0017.

[Slide]

I would like to now turn to the exploratory or subgroup analyses.

[Slide]

It is important to emphasize that this study was powered to test for statistical significance in the overall study population, that is, to test for the primary hypothesis or primary endpoint of all subjects. Nevertheless, it is important to explore various baseline characteristics such as lesion composition, lesion size, baseline vision, age, sex and pigmentation of the iris.

[Slide]

Despite a reduced ability to draw statistical conclusions because of decreased sample

size, in some cases as small as 18 patients, multiple subgroup analyses which can both lead to false positives and negatives--despite this no one subgroup drove the overall effect, as we will show you.

[Slide]

We will first look at the 0.3 mg and 1 mg doses as was described in the FDA briefing book. We have also analyzed and prepared the 3 mg dose and if people are interested later we can show you that. We will present this using pooled data because it was prespecified and we will show the individual trials after.

[Slide]

Here we can see for the pooled data at the 0.3 mg dose that in all cases of all patient characteristics the 0.3 mg active treated group did better than sham. This was for sex, age and, consistent with the biology of this disease and the mechanism of action of pegaptanib, for all angiographic subtypes, predominantly classic, minimally classic and occult, as seen here; also,

initial baseline visual acuity, size of the lesion, race and pigmentation of the iris.

[Slide]

Here we can see for severe visual loss--the first graph was moderate visual loss or primary endpoint, but we can see that the conclusions we made are supported by severe visual loss, or 6-line loss, 30-letter loss in this graph. The blue are the sham so all had more severe vision loss than actively treated 0.3 mg group for all patient characteristics. So, this supports our primary analysis.

[Slide]

Turning to the 1 mg group, we can see the same thing, that in all patient characteristics the 1 mg group did better than sham. Again, we can see that this information is supported by severe vision loss where, again, sham in all cases did worse than the actively treated 1 mg dose.

[Slide]

Let's now turn to the individual trials. Individual trials which are under-powered

inherently have more variability. Nevertheless, we can make the same conclusion, that no one subgroup drove the overall efficacy. Again, for trial 1004 with the 0.3 mg group we can see the very small Ns, sample sizes, for some of these groups and, again, we can see support for using severe visual loss as another important clinical endpoint.

[Slide]

For trial 1003, with the 0.3 mg dose we can see the same thing.

[Slide]

For the 1 mg dose, again we can see, in trial 1004, that in all cases the treated groups did better than the controls and this was supported by the severe vision loss in 1004 again.

[Slide]

And, in trial 1003, again, for moderate vision loss treated patients did better than the blue shams and support with severe vision loss where shams did worse than actively treated patients for progression to severe vision loss.

[Slide]

In order to be sure there were no important subgroup relationships, we also performed a multiple logistic regression to identify any potential factors either influencing the outcome or modifying the treatment effect. Subgroups and interactions of subgroups with treatment were investigated.

[Slide]

These are some of the subgroups that we evaluated, age, angiographic subtype, use of PDT, sex, race, lesion size, status of smoker/non-smoker, subretinal hemorrhage, the fellow eye vision loss and lipid.

[Slide]

We found for the 0.3 mg dose that no factors were identified as significant treatment effect modifiers for 0.3 versus sham, and no factors except treatment with pegaptanib were identified as significantly influencing the response, and this had a p value of 0.0003 in favor of treatment.

[Slide]

For the 1 mg group we again found that no factors were identified as significant treatment effect modifiers versus sham, and for pegaptanib at 1 mg there was a relationship between treatment with pegaptanib, again at 0.0001, and age which favored patients with less than 75 years of age. This is not to say that older patients did not do better. It just said that there was a favor for younger patients even both appear to respond.

[Slide]

What can we conclude from these exploratory or subgroup analyses? First, we have shown that the treatment benefit appears well-distributed among a broad patient population. Second, the efficacy is not consistently concentrated in or absent from any particular patient subgroup. No one subgroup drove the overall efficacy.

[Slide]

The 0.3 mg dose represents the lowest studied efficacious dose and it met its primary efficacy endpoint with statistical significance in

independent replicate trials, as we have shown you. The efficacy was substantiated in every clinically meaningful endpoint tested. We have seen the secondary endpoints. And, the 1 mg and 3 mg doses show no additional benefits over 0.3 mg. Tony will shortly show you that there was no safety difference between 0.3 mg and 1 mg as well. However, theoretically we all know that a lowest dose yields the lowest systemic concentration. So, the sponsor advisory board and independent data monitoring committee endorsed the 0.3 mg dose as a dose that should be selected.

[Slide]

I would like to turn now to angiographic findings. We have mentioned to you that we believe there are two mechanisms of action for pegaptanib, anti-angiogenesis and anti-permeability. As I will now show you, we have anatomical confirmation for both mechanisms of action that support the visual findings we have shown you today.

Let's first look at the anti-angiogenesis. Here is a patient in the trial with predominantly

classic neovascularization that showed virtually complete regression. The white large area is the neovascularization. You can see it has almost completely regressed after 54 weeks of treatment. But this is one case. So, let's look at the whole group.

[Slide]

What we can see is that there was a decrease in the lesion size that had a low nominal p value in favor of active treatment for the 0.3 and the 1 mg dose. So, we have anatomical confirmation or support for anti-angiogenesis as a mechanism of action that supports the visual findings.

[Slide]

The second mechanism of action that we described was anti-permeability. Here is another patient in the trial that had significant cystoid macular edema with neovascular disease. We can see the cystoid-like patterns here. This is a sign of a lot of permeability. After 54 weeks of treatment we can see a great decrease in the permeability.

[Slide]

Again, we can show that leak size over time was less for treated groups than for shams. The p values here are noted.

[Slide]

In addition, we can look at the change in leakage to week 54 as a sign of anti-permeability action, and we can see that very similar to visual distribution curves I showed you earlier, we can see again that there was less leakage noted more often in actively treated 0.3 mg patients than in sham, and more leakage noted in shams than in actively treated eyes. This change in distribution had a low nominal p value of 0.0004. So, again we have anatomical confirmation for anti-permeability as an important mechanism of action that supports the visual findings.

[Slide]

I would like to now turn to photodynamic therapy, or PDT. I think it is first important to have a historical perspective of the use of PDT in this trial so you can understand some of the

challenges we faced when we were designing this trial.

At the time of starting the trial PDT was available primarily in the U.S., and there were certainly ethical considerations that required that PDT be permitted in patients with predominantly classic disease. However, the PDT usage pattern was not yet known.

[Slide]

So, what we decided to do was to create very strict rules for the use of PDT in this trial. What that meant was that patients had to have predominantly classic disease and the masked physician--remember, we had two physicians--the masked physician determined if the patient was eligible for PDT per the FDA label and then whether that PDT was recommended for that individual patient. If so, the treatment was administered per the FDA label.

Now, to ensure that these strict rules were being followed, we had a reading center review the usage pattern and we found that 92 percent of

the time the reading center agreed with the appropriate use of PDT in this trial.

[Slide]

PDT use could occur three ways: prior to the study, at baseline, and post-baseline and, actually, any combination of the three. It is important to emphasize that overall the use of PDT was extremely low. Three-quarters of patients were never exposed to PDT in the study eye at any time in the time trial.

[Slide]

Let's examine each one of these three scenarios in detail. First let's talk about prior PDT which was stratified and was balanced at randomization. Also, notice the small numbers again, emphasizing very little PDT use in the trial, 18-29 eyes in the various subgroups, but it was stratified and balanced.

[Slide]

Baseline PDT is the second scenario, and the baseline PDT use was again very similar among the groups. We can see here that for the active

treated groups 10-13 percent of patients had PDT at baseline compared to 14 percent for shams and, again, look at the very small numbers, 31 to 40 patients per subgroup.

[Slide]

Finally, let's talk about post-baseline PDT use. Now, it is important to mention that a meaningful analysis of potential post-baseline PDT effects on efficacy is limited to the inherent bias in the trial. What I mean by that is, remember, the patients were never randomized to post-baseline PDT use. In order to really assess the baseline PDT use we would have had to design a trial randomizing patients to PDT and baseline. That wasn't this trial. As an example of this, what is called the channeling bias, a patient with a poor response might be the patient that would be preferentially channeled to get PDT. What this really means is that post-baseline PDT is an outcome variable. So, for this reason, we must treat post-baseline PDT in a different way, as I will show you now.

[Slide]

We need to ask was there increased PDT use in pegaptanib patients relative to sham that could suggest that some of the pegaptanib efficacy was derived from PDT?

[Slide]

The answer to this question was no. As we can see, there was no higher use of post-baseline PDT in active treated patients compared to sham.

[Slide]

The second important question about post-baseline PDT use is was there an increase in the average number of PDT treatments in pegaptanib patients relative to sham?

[Slide]

Again the answer is no. As we can see again, there was no higher post-baseline PDT use in active treatment eyes compared to sham.

[Slide]

The third important question, which will be addressed in detail in Tony's safety section, is was there evidence of any adverse events with the

co-administration of photodynamic therapy and pegaptanib that could lead to a drug-to-drug interaction? The answer is no--more on that in just a few minutes.

[Slide]

In summary, pegaptanib met a clinically meaningful primary efficacy endpoint with statistical significance in replicate, independent, well-controlled clinical trials.

[Slide]

I will now ask Tony to come up and discuss our clinical safety database.

Pegaptanib Clinical Safety

[Slide]

DR. ADAMIS: This is the entire safety database. This includes the patients from the earlier Phase I/II trials. What you see here is that the total clinical experience to date includes over 1,200 patients in over 10,000 treatments, of which 7,500 are intravitreous injections that we can monitor for the safety. There is a slight imbalance that you will see in that there are more

patients receiving 3 mg than 1 mg of 0.3 mg. That is because that was the dose that was used throughout most of the Phase I/II program. In addition, we gave doses of 0.25 mg and 2 mg in those earlier programs as well.

[Slide]

The overall safety is shown here. As regards any adverse events, you can see it is balanced between all treatment arms and sham. There is an imbalance in the serious adverse events. These are largely injection related, and we will talk about those in depth in a moment.

The discontinuations, you will note, due to adverse events are low. They are one percent in both the treated and the sham arms. Similarly, the death rate is balanced to two percent.

[Slide]

Looking at the death rate just a little more closely, we can see that there is no evidence here of a dose response.

[Slide]

Let's look at the most frequent non-ocular

serious adverse events. This is a busy slide but the thing to note here is, first, that there is good balance between the treated and the sham arms and, secondly, there is no clustering within a system organ class. This is rather diffuse. These conditions are age appropriate. The mean age of this population is 77 years old that we studied. These people had a number of concomitant illnesses. Fifty percent of them had hypertension; 25 percent were on statins; 20 percent had cardiac disease. So, we believe it is representative of the population.

[Slide]

We looked particularly for VEGF inhibition-related adverse events as these have been reported with other non-selective inhibitors given intravenously at higher doses. We were happy to see that there were no signals here. The most sensitive signal, the one that has been picked up with other non-selective inhibitors in smaller trials than ours, less powered but nevertheless it was evident, was hypertension. You can see here

that the rate of adverse events is 10 percent both in the treated and in the sham arms--no signal there for that very sensitive signal of VEGF inhibition. Thromboembolic adverse events are similarly balanced, as are ischemic coronary artery disorders, heart failure and serious hemorrhagic adverse events.

[Slide]

Why is it that we did not see any of these VEGF inhibition-related phenomena? There is a number of reasons. Some of these are theoretical, some are real but in aggregate they provide I think an argument. Pegaptanib is, as I said, selective for VEGF 165 so the other major isoform 121 is never blocked. So, all VEGF is never blocked with pegaptanib, even if you gave it at very large concentrations. It just does not bind to VEGF 121.

Secondly, the concentrations that we see when we put 0.3 mg in the eye are many orders of magnitude less in the plasma and those concentrations are below the inhibitory concentration that our models have told us both for

in vitro and in vivo inhibition of VEGF. So, we believe that these are levels that are below the ability of pegaptanib to affect VEGF levels in any sort of substantive way.

Third, as I just said, there was an absence of sensitive VEGF inhibition signals, the most sensitive being hypertension which I showed you but also in our 1006 trial, where we looked carefully at proteinuria, again there is no evidence that this drug is inducing proteinuria in either our clinical population or in our preclinical models.

Then, the report recently of thromboembolic adverse events occurring in cancer patients on chemotherapy and receiving Avastin--we think there are a couple of very different things about our population and that population that was studied. Number one, cancer in and of itself predisposes patients to thromboembolic phenomena. They have indwelling catheters; they are bedridden; and the cancer itself alters the clotting system. Secondly, some chemotherapy has been shown to be

vascular toxic, to be prothrombotic. There is a published literature on that.

So, add these two hits to the vasculature and then block all VEGF to prevent the endothelium from healing itself, one can have a theoretical basis for understanding now why thromboembolic phenomena may be more prevalent in a population with cancer and chemotherapy. That is not age related macular degeneration. This is a very different population that is not, by and large, on chemotherapy and do not have cancers.

[Slide]

Let's look at the ocular adverse events. Again, this is a busy slide but we will talk about these events in a little more detail. They are listed here, those that occurred greater than or equal to 10 percent of patients on either pegaptanib or sham. You can see that there is a slight imbalance in eye disorders, and we will talk about these, and you see a number of various adverse events listed here.

[Slide]

Let's talk about them in more detail, number one that was listed on the previous slide being eye pain. These patients receive nine intravitreous injections over the course of a year. It is rather remarkable actually that two-thirds of them never reported a single instance of pain. Of those patients, approximately the one third that did report pain, it was mild or moderate in character in 99 percent of them, and only one patient exited this trial describing an adverse event of pain.

The other important thing to note here is that the eye pain in the sham arm, at 28 percent, was significantly higher than what is seen in the fellow eye, 2 percent. So, some of this mild pain that these patients experienced--one conclusion you can draw is that it may be due to the preparative procedure prior to the injection of the drug. As you recall, these patients have a speculum placed in the eye. They have povidone-iodine scrub. They have a subconjunctival anesthetic injection. These things may have contributed to the lion share of

the reports of pain which, again, was mild. Then, obviously, there is a difference here. The remainder of it here can well be ascribed to the actual intravitreous injection itself.

Of those patients who reported pain, it was in a minority of their injections, two in both the treated and the sham arms, and the median time to resolution was two to three days which is the time of the follow-up phone call.

[Slide]

With regard to vitreous floaters, there was more than an imbalance here. It was 33 percent in the treated arms versus 8 percent in the sham. Again, there is a slight difference, 8 versus 1, between the sham eye and the fellow eye so some of this may be due to the preparative procedure but a large portion of it, the majority of it, is very likely due to the act of giving an intravitreous injection itself. When giving a 90 mcL volume injection into the eye, in the average human a volume of 4 mL, you are displacing the vitreous and it is perhaps not surprising that as a function of

that you are going to induce floater. These floaters never were severe. All of them were characterized as mild to moderate. No patient left the trial because of floaters. It was in a minority of injections, 1 to 2 injections, that these were reported, if they ever were reported, and the median time to resolution was 3 days in the treated arms versus 7 days in the sham arms.

[Slide]

We looked at cataract very carefully. We specifically looked at cataract in only the aphakic eyes. One-third of these patients approximately were pseudophakic. What we saw was that across all treatment arms there was a slight imbalance, with 30 percent of the eyes having an adverse event of cataract versus 26 in the sham arm. This slight imbalance may be partially explained by the fact that the phakic fellow eye also had a slight imbalance, 17 percent in the treated versus 15 percent in the sham arms.

But we looked at this a little more in depth. The type of cataract that one would expect

if this was due to a drug toxicity, the type that has been amply described in the literature, is posterior subcapsular cataract. So, when we looked for that specific type of cataract grading, you can see there is zero difference. It is 11 percent in both the treated and the sham arms.

[Slide]

Nuclear cataract was similarly well balanced. In fact, if you remove the eyes that were vitrectomized, which we will talk about in a minute, vitrectomy can cause a nuclear sclerotic cataract to accelerate. This is 18 percent in both arms and there is, indeed, a slight imbalance in cortical of 18 versus 15 percent.

One piece of objective data we have is that the vast majority of these patients came in at baseline with cataract and only 3 patients underwent elective cataract surgery over the 54 weeks of the trial in the treatment arms.

[Slide]

Anterior chamber inflammation was another adverse event. You can see here that there is an

imbalance slightly with 14 percent occurring in study eyes versus 6 percent in the sham eyes, and there were zero reports in the fellow eyes. None of these cases of anterior chamber inflammation were characterized as severe. All of them were mild to moderate and we believe they were largely due to the active intravitreous injection and not to the drug itself. The reports of inflammation were all moderate and self-limiting and did not increase during the course of the trial. In fact, there was a slight trend to decrease, arguing that there wasn't a sensitization to the molecule here, in fact, supporting that this was due to the injection itself. The median time to resolution was 8-9 days, and no patient left the trial because of inflammation.

[Slide]

We looked at interaction potentially with PDT and specifically at ocular adverse events. You can see here that the majority of patients did not have the combination of PDT and pegaptanib, but of those who did we looked very carefully at the event

rates and the important thing to consider here is the event rate difference in the sham arms plus/minus PDT, and does that difference change in any sort of meaningful fashion when the PDT is given together with pegaptanib. The answer is that from these data there doesn't appear to be a difference in those two measures. The same is true with vitreous floaters. There is a slight difference here and there is really no difference here in the treatment arms.

[Slide]

But let's look at it another way. This assessment is looking to see if there was a report of an adverse event at any time during the 54 weeks. For instance, if the patient had PDT at baseline but had an adverse event at 54 weeks it would be captured and presented in these data. We thought we would try to look at this a little more carefully and see if there was a better temporal relationship. So, now we are looking at data of patients who had PDT plus/minus 2 weeks around an injection of pegaptanib. These events may more

likely signify some sort of interaction and, again, there are no alarming signals here.

When one looks at eye pain there is very little difference here and there is very little difference here between the sham and the treatment arms. The same is true for corneal epithelium disorders. For these two specific adverse events one can postulate a mechanism as to why that is. There is, you know, the povidone-iodine prep for the injection which can affect the epithelium and perhaps cause pain. On top of that is a near temporal relationship the placement of a contact lens for doing the PDT, and one could understand why there might be a slight increase here. Again, no patients dropped out because of any adverse events related to a combination of PDT and the use of pegaptanib.

[Slide]

Now let's concentrate a bit on ocular serious adverse events. The three most common we are going to discuss in detail here are endophthalmitis, retinal detachment and traumatic

cataract. The ones below occurred at a very low event rate. When the narratives in the cases were looked at in depth there really did not appear to be an association with the use of pegaptanib so we will not discuss them further here unless you wish to discuss it later in the question and answer session.

Endophthalmitis occurred in 12 patients over 54 weeks. That translates to a relative risk of 1.3 percent of patients developing endophthalmitis over the course of one year of therapy. So that we could compare our rate to the published literature this was converted to a per injection rate of 0.16 percent. What we learned is that the rate that we saw is not an outlier; it is within the published norm and reported norm in cases of endophthalmitis in patients receiving intravitreous injected therapeutics.

As important as the rate is what happened to these patients, what was the outcome. One patient lost severe vision in this trial as a function of their endophthalmitis, 1/12, which

translated to a rate of 0.1 percent over the course of the year. Seventy-five percent of the patients who developed endophthalmitis elected to stay in the trial.

Traumatic cataract--you can see there were five cases of it and there were five cases of retinal detachment, of which three were rhegmatogenous in nature.

[Slide]

I show you here the specific details of all 12 cases of endophthalmitis. What you can see here are the starting visions, the visions prior to the event, and the change in vision from just prior to the event which probably most accurately captures the visual loss related to the endophthalmitis itself. What you can see is the one patient who lost 11 lines as severe vision loss.

Let me just tell you anecdotally what happened. It was a protocol violation. It turns out this patient had an active lachrymal sac infection prior to the development of the

endophthalmitis and the injection of the mediation, and had an active lachrymal sac infection after the event of endophthalmitis. The patient should never have been enrolled because that was an exclusion criterion.

The other patients, as you can see, were treated aggressively and their visual outcomes tend to be perhaps a bit better than what you would expect for a case of endophthalmitis. In fact, there are some patients here who gained one or two lines of vision.

[Slide]

How were these patients diagnosed, and were we able to identify the endophthalmitis relatively early? This slide shows you exactly what happened. Three patients were identified in their follow-up phone call at days three-four post injection. Eleven patients presented to their physician's office with complaints, and this happened between days two and five. Two patients came in and were diagnosed in a routine follow-up. The endophthalmitis cases I am describing here are

the 12 in the first year and the ones that have occurred subsequent to that which I am going to talk about.

[Slide]

We have been following the endophthalmitis issue very carefully and I would like to provide you with an update on where we are beyond the 54-week time period. As I just said, in the first year 0.16 percent of injections, or 1.3 percent of patients, developed endophthalmitis. In the second, and now some patients have entered the third year of this trial, there have been five additional cases as of July 31st of this year, and there has been one case in our Phase II diabetic macular edema trial. So, if you look at the total now, it is 18 cases of endophthalmitis with a denominator of over 14,500 injections, and the rate now is reduced somewhat to 0.12 percent per injection.

In the first half of this trial when we saw the case reports of endophthalmitis we convened an expert panel of ophthalmologists and retinal

specialists who work in the endophthalmitis area and we decided that we needed to heighten the awareness of the need for strict adherence to an aseptic protocol when one is giving an intravitreous injection. In fact, there was a letter sent to IRBs and a formal protocol modification mandating the use of a sterile drape, of a speculum, of the use of povidone-iodine. When we did these things and we analyzed what the potential effect could be, what we saw was that prior to that protocol modification being adopted at all sites between August of 2001 and May of 2003 the rate was 0.18 percent, and after that protocol modification the rate has now fallen to 0.03 percent.

Can we ascribe the decrease in the rate to the change in the protocol? Not necessarily. There was more than one variable that was changing here. At the same time that we instituted this protocol modification and heightened awareness about the aseptic technique there was a dramatic uptake in the number of intravitreous injections

being given for off-label use in diabetic macular edema with steroids, triamcinolone in particular. So, the knowledge base and the experience of retina physicians increased rather dramatically at the same time that we saw a drop in our rates.

[Slide]

The visual outcome for the cataract cases is shown to you here. For the one patient who lost 7 lines of vision, it was ascribed to progression of macular degeneration. All of these patients, in fact, had successful cataract surgery.

[Slide]

The visual outcome of the retinal detachment cases is shown here. All of these were successfully repaired and you can see the cases of rhegmatogenous detachment which most likely were injection related. The visual outcomes were quite good.

[Slide]

Intraocular pressure was examined. As I said earlier, it is not surprising if one injects 90 mcL into a 4 mL closed space that you will see a

transient rise in pressure. In fact, in ophthalmology it is common with almost all procedures that pressure spikes tend to occur. Well, they occurred here and the transient rise in mean intraocular pressure at the first prespecified measurement, 30 minutes, was 2-4 mm across the treatment arms.

It is important to note that the mean intraocular pressure returned to pre-injection levels one week following the injection, which was the next visit, and that 90 percent of patients, approximately 90 percent of patients, never had a spike above the prespecified threshold of 35 mm and any patient who did have a spike was not allowed to leave the physician's office till the pressure was below 30 mm.

Very importantly, there was no evidence of a persistent increase in intraocular pressure over one year. The drug did not seem to alter the outflow of the eye in any way. In those patients who did have a spike, the question was if you had a spike was it because somehow the drug was altering

the outflow mechanisms, and if that was the case you would expect to see an increased incidence during the course of the trial as it progressed. As the data show you here, that is not the case. It doesn't appear to increase over time and, in fact, may have been dropping slightly.

[Slide]

This slide simply shows the mean intraocular pressure values over time for all three treatment arms and sham, again giving us some confidence that the drug is not inducing a rise in chronic IOP.

[Slide]

We have a safety update for you regarding angiography. Colored photographs and angiograms were looked at in the independent reading center at the University of Wisconsin. We have looked at up to 97 percent now of our month 18 angiograms and 92 percent of our two-year angiograms to get a sense of is there any evidence of cumulative toxicity. The results are that there is no evidence whatsoever of alterations in the normal retinal or

choroidal vasculature as a function of the drug being in the eye now for up to two years, nothing that deviated from the natural history of age-related macular degeneration and no alterations in the normal vessels.

[Slide]

The safety update, which was just concluded in the past week by the independent data monitoring committee, has reviewed 100 percent of the patients through month 18 of this trial and 97 percent through month 24, and there have been no deviations from sort of the pattern of adverse events, the ones that we saw in the first year of the trial. There have been no new safety concerns except perhaps for a slight increase in the number of retinal detachments. There were 6 that were reported in the second year of this trial.

[Slide]

To summarize the non-ocular safety, there was a very low discontinuation rate due to adverse events. It was one percent and it was balanced in the treated and the sham arms. Non-ocular serious

adverse events appeared to be similar in rate and character between pegaptanib and sham, and the mortality rate, as you saw, for the 77 year-old population was similar between pegaptanib and sham.

[Slide]

As regards ocular safety, I think what we can conclude is that the majority of the ocular adverse events were judged to be procedure related. They were transient and mild in character and largely self-limiting. There was a low discontinuation rate due to ocular adverse events and the serious adverse events were infrequent. They were rarely associated with severe vision loss and were mostly procedure related. Finally, there were mild transient and predictable, manageable increases in intraocular pressure but no evidence of a long-term rise in intraocular pressure.

[Slide]

At this point Prof. Don D'Amico, who is a practicing retinal specialist at the Massachusetts Eye and Ear Infirmary, will come and discuss the risk/benefit profile for pegaptanib.

DR. D'AMICO: Thank you, Dr. Adamis. Dr. Dunbar, members of the advisory committee, ladies and gentlemen, with your permission I would like to introduce myself a little more fully and my perspectives so that you can have the clearest context in which to place my remarks.

[Slide]

With regard to this study, while it was in progress I was invited to be a member of the safety committee and later became its chair. At the conclusion of the study I was asked to be a member of the scientific advisory board. I perform a virtually identical role for the Alcon Corporation, chairing their safety committee in the evaluation of their anecortave product. I also advise them on surgical themes and instrumentation as well. Finally, I am a consultant to the Iridex Corporation serving as a member on the safety committee for the transpupillary thermotherapy trials and their PTAMD or laser for drusen trial. I hold no equity in any of these companies nor any

of their competitors.

[Slide]

I would like to also share four perspectives that will inevitably influence my remarks and may be helpful to you also in your evaluations. First, of course, I was a member of the pegaptanib safety committee. Secondly, I have had a career-long laboratory, as well as clinical, interest in endophthalmitis and the effects of administration of intravitreal medications. I am, as introduced, an academic in the field of retinal diseases and therapy. But perhaps most importantly and most germane is that I have a very active retinal practice at the Massachusetts Eye and Ear Infirmary and care for many patients with macular degeneration.

[Slide]

As has been said, neovascular AMD is quite a source of human suffering. At the 20/40 level of visual acuity driving privileges frequently become impossible for a patient. At 20/80 or worse difficulty is even present in trying to read large

print. And, 20/200 or worse is a commonly accepted level of definition of legal blindness at which it is difficult to recognize faces and independent function is threatened.

[Slide]

How extant is this problem in the world today? In a very careful meta-analysis of the most comprehensive studies recently reported by the Eye Diseases Prevalence Research Group, they looked at studies in the United States, Western Europe and Australia over an 11-year period.

[Slide]

Based on their analysis, it is the leading causes of blindness in U.S. adults in patients aged 40 years or older. You see that slightly over half are due to age-related macular degeneration.

[Slide]

They then applied their model to the U.S. Census data for both 2000 and projected to the future. In a morning filled with numbers, I will spare you all the numbers here, but using a definition of 20/200 or worse as blind and 20/40 or

worse as visually impaired, there are 3.3 million Americans with visual impairment today. In the future there will be approximately 5.5 million American with visual impairment at some level, again slightly over half, due to age-related macular degeneration. So, it is clearly a problem.

[Slide]

As such, it merits our highest attention as physicians, researchers, etc. to try to find treatments and even cures. This slide is color coded and it lists the candidate therapies for neovascular subfoveal age-related macular degeneration. Therapies which have demonstrated effectiveness in replicate clinical trials are shown in yellow. We have laser photocoagulation, photodynamic therapy with Visudyne and the data you have just heard on pegaptanib. The great majority of interventions are listed in white, which indicates ongoing study with various degrees of promise, and it includes surgical options, as you see here and a variety of other laser treatments, as well as other pharmaceuticals, many of which are

nearing the end of their clinical trials. There are also some abandoned therapies that were ineffective and combination strategies, as you see in the lower right, are becoming of increasing interest.

[Slide]

Looking at the established therapies, there are two. One is photocoagulation with thermal laser which has been effective in extrafoveal, juxtafoveal and subfoveal lesions. However, in subfoveal lesions this therapy has been abandoned due to the immediate destruction of central vision following treatment and is no longer in clinical use. Photodynamic therapy with Visudyne is approved for subfoveal predominantly classic lesions.

[Slide]

In addition, evolving clinical practice, in a hope to provide improved care for patients with macular degeneration, has led to a new accommodation therapy which has become widespread. That is the combination of a PDT treatment with

Visudyne in association with an intravitreous induction of triamcinolone in the peri-PDT period. This treatment has had some very promising early pilot results but the literature is quite minimal at present. Nevertheless, it has become a common treatment in clinical practice.

[Slide]

Intravitreous injections are quite common in my world as a retinal specialist. They were employed and were actually the pathway to great success in the therapy of endophthalmitis, and are still continued widely in use for that indication. We also utilize intravitreal injection as a treatment of retinal detachment, as well as administering agents for CMV retinitis. However, there has been great expanded use recently in office practice of intravitreal injections as regards the use of triamcinolone acetodine for diabetic macular edema, retinal vein occlusions, uveitis, as I have just mentioned, in association with photodynamic therapy.

[Slide]

Pegaptanib represents the potential for a new approach, a pharmacotherapy, and what are the advantages of pharmacotherapy? They are both general and specific. In general, pharmacotherapy offers the prospect of treatment at a molecular level with improved targeting of the disease process and, more importantly, limitation of the collateral damage that invariably occurs with larger scale interventions such as surgery or laser.

Pegaptanib quite specifically is based on very extensive basic science into the most widely accepted, central disease processes in AMD, namely neovascularization and leakage, with consistency across multiple experimental models and studies.

[Slide]

As a member of the safety committee, we looked for three specific areas in great detail. One, were there any potential systemic side effects from receiving an anti-VEGF medication? Secondly, were there intraocular drug-related side effects from this VEGF medication? Thirdly, were there any

mechanical side effects or complications from the intravitreal injection procedure itself?

[Slide]

We did find serious ocular adverse events related to the injection procedure. As you have heard, there were 12 cases of endophthalmitis. This incidence rate is quite comparable to that in published series for intravitreal injection with the other forms of intravitreal injection therapy that I have mentioned previously. One of these patients had severe visual loss. Nine of the patients continued in the study and elected to continue receiving study medication. Finally, after protocol modifications, the incidence is clearly trending downward.

There were five cases of retinal detachment, which were repaired and some were related to the underlying macular degeneration itself. Traumatic cataract was seen in five cases and all were surgically repaired without sequelae.

[Slide]

So, in these 22 serious ocular events, we

considered them in the context of 7,545 intravitreous injections performed in 1,190 patients by 117 centers worldwide, and many of those centers had more than one injector. We felt that this denominator indicated substantial safety for this procedure.

We also found no evidence of systemic side effects, no evidence of ocular drug-related side effects, and the majority of other adverse events were mild and transient within the eye. The serious ocular adverse events were infrequent and manageable. So, we concluded that there was a very favorable safety profile that, in addition, may be further improved by education and additional training.

[Slide]

If we look at severe vision loss, again to understand the context of these adverse events, if a patient presented to the trial and received sham, that is, usual care, there was a 22 percent risk per year of suffering severe visual loss. When they were enrolled in the pegaptanib group that

risk was reduced to 9.5 percent per year.

[Slide]

In the endophthalmitis, retinal detachment and cataract serious ocular events that we saw, the risk of severe vision loss, that is 6 or more lines of vision, was 0.1 percent, indicating substantial order of magnitude less risk from endophthalmitis than from the real problem here which is the macular degeneration itself.

[Slide]

Regarding efficacy, you have heard a detailed presentation and I will just summarize. There was significant reduction in moderate and severe vision loss compared with sham. There was promotion of vision stability and gain in a proportion of patients. There was efficacy with broad-based entry criteria including a range of subfoveal neovascular AMD lesions. And, the benefit of intravitreous pegaptanib therapy was early and sustained.

[Slide]

As we have seen, in this slide baseline

visual acuity is on the left. Sham is indicated in purple and pegaptanib in grey. At 54 weeks there is a definite shift in the 0.3 pegaptanib group to preservation of better vision on the left of this chart compared to the visual acuities observed with sham.

[Slide]

I am not a biostatistician but I will try, for myself and for all of us, to place these results in some kind of a wider context. What could this mean? No one knows exactly how many new subfoveal neovascular lesions occur a year, but 120,000 per year of new treatment-eligible patients is probably a reasonable estimate. If those patients were to behave similar to the gathered group enrolled in this trial, we could make some statements, and here they are:

Pegaptanib potentially prevents severe vision loss, that is a loss of 6 or more lines of vision, in 15,000 additional patients per year in the United States compared with usual care, based on a 57 percent reduction in the rate of severe

vision loss with pegaptanib.

[Slide]

Secondly, reaching a level of 20/200 or worse within the treated eye, we could call that blindness in the treated eye. Pegaptanib potentially prevents treated-eye blindness in an additional 22,800 patients per year in the U.S., again compared with usual care, based on a 38 percent reduction in the rate of treated-eye blindness with pegaptanib.

[Slide]

In conclusion, from the perspectives available to me and now available to you, I have concluded that pegaptanib will have a significant impact on AMD in regard to both individual patients with AMD lesions that would become amenable to treatment and, secondly, in its effects on visual function and its preservation in the aging U.S. population.

The positive results in this trial indicate the beginning, and not the limit, of pharmacotherapy for AMD. I agree with the

sponsor's recommendations that the benefits of pegaptanib therapy for AMD strongly outweigh the risks. Thank you.

Committee Discussion

DR. DUNBAR: Thank you to the sponsor and Drs. Guyer, Adamis and D'Amico. At this point I would like to open the floor for discussion and questions for the sponsor from the committee members, and ask that you will speak your name into the microphone as you ask each question. Are there any questions from the committee members? Dr. Chinchilli?

DR. CHINCHILLI: Yes, I don't know much about the disease and the patients that were recruited for the two trials so, please, bear with me. Could patients have AMD in both eyes? I mean, roughly what proportion of patients that were in the trials had that situation?

DR. GUYER: In general, for neovascular age-related macular degeneration usually one eye becomes active at a time. If the patient lives long enough, they often will get it in the second

eye. In this particular trial the investigator would choose--in a very few number of cases where there would be active disease that was eligible for the trial, the doctor would make that decision. If we look at slide D-82--

[Slide]

--here we can see some of the baseline characteristics. In two-thirds of the patients this was the worse eye that was treated. Again, no patient was treated in both eyes at the same time. But in the lifetime of a patient there could be some overlapping times where they have an active lesion and the second one becomes active. Some patients are fortunate enough not to get it in their second eye but, unfortunately, if they live long enough many will.

DR. CHINCHILLI: Thank you.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: A superb presentation; very interesting results. Just two questions. Number one, glaucoma was not an exclusion criterion in the study. So, some of the patients had glaucoma and

AMD. Do you have any data as to the effect of chronic injections on the small subgroup of patients that had glaucoma?

DR. GUYER: I will let Tony answer that.

DR. ADAMIS: We were interested in that question as well. Slide OS-31.

[Slide]

We looked specifically at patients with a history of ocular hypertension and/or glaucoma, and then followed their pressures throughout the entire 54 weeks. What we saw was that there was no change in their intraocular pressure as a function of treatment.

DR. PULIDO: The other question probably is to you as well. There are some recent articles--here is one from Nature, May: VEGF delivery with retrograde transported Lentivector prolongs survival in a mouse ALS model. Here is another one: mural protection of ischemic brain by VEGF is critically dependent on proper dosage. Here is another one. So, we have gone under the assumption that VEGF and VEGF 165 is specifically a

cytokine for angiogenesis, but there is more data to show that there is an independent effect directly on neural tissue, separate from its angiogenic effect. ERG was not a part of this trial. You did some ERGs on some dogs, from what I saw here. I don't know how many, how long, etc.

So, considering the neuroprotective effect, from your data--it is wonderful--that the angiogenesis is important, critical to take care of this significant problem in patients. But my concern is the long-term chronic dosaging considering that there is an independent effect of VEGF as a neuroprotective agent.

DR. ADAMIS: As always happens in science, what seems very straightforward becomes more complex, and what you quote is absolutely correct. I think that is Peter Carmeliet's paper in Nature. But what has been learned in about the last five years is that neural cells have VEGF receptors and VEGF may be neuroprotective for certain tissues. Certainly, in the ALS model that is the most convincing story to date. Whether the effect is

direct or not is still being debated in the scientific world, but it may well be direct because of the VEGF receptor on the neural cells.

We were interested in this as well. Even before we got into the scientific question as part of our preclinical safety testing, there was a 9-month dog study where the dogs received 3 mg injections every 2 weeks bilaterally. Then they had ERGs done and there were no abnormalities seen there. So, that gives us a little bit of comfort but, more importantly, recently we examined this issue and looked specifically at the isoform story. We presented a paper at ARVO last spring where we showed that in a model of retinal ischemia if one gives a pan-isoform, non-selective VEGF inhibitor, you can in fact induce some neural apoptosis. But when we gave pegaptanib in the exact same setting there was no induced apoptosis. So, again getting at this thesis, the important thing with pegaptanib I think is that you are sparing some VEGF to allow it to have its physiological or perhaps these rescue functions that can occur in the eye. So,

that gave us an additional measure of comfort that we are not going to have neural toxicity.

DR. PULIDO: But the question still arises have you done long-term ERG studies on these patients?

DR. ADAMIS: Oh, I am sorry, no, we have not done those in these patients.

DR. DUNBAR: Mr. Kresel?

MR. KRESEL: My disclaimer is that I am not a statistician and so I am not sure if this is even an appropriate way to ask this but I am going to ask it anyway. You did a great job of looking at endophthalmitis which, you know, obviously is one of the things that people have concern about, and referred to a decrease in patients that was only five cases in years two and three. My question is how many patients continued therapy that far? So, did the number of patients decrease and, therefore, the percent not go down? Because what we saw is a cumulative number that, of course, did go down.

DR. ADAMIS: It is a fair question. The

number of patients was decreased in the second year. That is why the metric we used was on a per injection basis. That accounts for any loss of patients and those were the rates that I presented to you today. So, on that basis it does go down. Slide 129.

[Slide]

Just to show you the data, you can see that prior to the amendment on a per injection basis it was 0.18 percent, and then post the amendment it was 0.03 percent but with that additional confounding variable of a lot of off-label steroid injections going on.

DR. DUNBAR: Dr. Gates?

DR. GATES: In the context of the cases of endophthalmitis, could you expand on the initial injection technique versus some of the changes that you made secondarily? Because draping oftentimes means different things to different people.

DR. ADAMIS: Correct. The details of the injection procedure are on a slide but let me see if I can recite them from memory for you, the

changes. There was a requirement for the installation of an antibiotic drop or dilated povidone-iodine prior to the amendment. Then, after the amendment the drape that was specified is a clear plastic one that adheres around the lids and the lashes, and then the placement of the speculum, and then also asking for a povidone-iodine flush to be done, and then patients received postoperative antibiotics. So, what we tried to instill there was a sense of uniformity in the procedure. There was more latitude prior to that. Those were the changes, to the best of my memory, that were instituted.

DR. DUNBAR: We have more than one-year data, but would you anticipate that the patients will continue every six-week intravitreal injections for the rest of their lives?

DR. ADAMIS: That is an important question. It is one of the questions we ask in the second year of the design. We want to know, obviously, about the safety in the second year and then an important question was do people need to be

on this for the second year. So, the trial design is one of randomized discontinuation to try to get to an answer as regards that very important question, do people need another nine injections?

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I noticed in the data that most of the p values were significant, at least in the graphs and the tables, for the 0.3 mg and the 1 mg doses, and for the higher dose there was less incidence, at least in the tables and graphs, of statistically significant levels. Are there any conclusions you have drawn about that? Is more not better, etc.?

DR. GUYER: It is a great question and obviously one we spent a great deal of time analyzing. There really is no definite answer to why the 3 mg, as you mentioned, perhaps appeared not to do as well. Slide E-51, please.

[Slide]

There is one possible explanation that we have looked at. This shows the mean change in vision over time for each individual trial. On the

left is study 1004, on the right is study 1003. What you can see is that in one of the trials, 1004, this is the 3 mg dose, this is the 0.3 mg and 1 mg dose, going head-to-head pretty throughout. Of course, here is the usual care sham. It seemed that the 3 mg dose in one of the trials didn't seem to do quite as well as the other two active treatments--still doing better than the sham. In 1003 you can see that actually all three doses seemed to do equivalently.

So, one possibility is, you know, six different events, three doses, two trials, one out of six times by chance, it is possible that the 3 mg dose didn't do as well. Of course, as you mentioned, all of these clinical parameters, secondary parameters, etc., are all dependent on the other. That is one explanation.

The thing that we do know, however, is that the 0.3 mg dose, which represents the lowest efficacious studied dose, clearly hit the primary endpoint in replicate trials and showed consistent behavior throughout the trials. Because of safety

issues, theoretical safety issues, we believe that the 0.3 mg dose has met the requirements to be an effective treatment here.

DR. DUNBAR: Dr. Miller?

DR. MILLER: Thank you. In terms of the number of patients that have been in the trials, are you comfortable or is the model sufficient enough to tell us that there are no adverse risks related to the population? For example, with Vioxx we now know that after a period of time there are now people that are coming up with cancer, that it is causing cancer in some of them. Have you given it to enough patients so that you would know if there were rare cases where other problems would be caused?

DR. ADAMIS: The population studied was large in that it was 1,200 patients, large for an ophthalmology trial. But for very rare events, and this is a problem faced with all clinical trials, that show up in patients on the order of one in every 10,000 or so, you just don't have the power in these types of trials to detect in a very

air-tight manner those signals.

That being said, with the power we have, and we do have some significant power according to the guidelines Dr. Chambers talked about earlier, we were happy to see with all three doses that there wasn't any evidence of toxicity, either systemically or in the eye, related to the drug. But we will never know with absolute certainty for those very, very rare events.

DR. MILLER: Thank you.

DR. GUYER: Also as Dr. Chambers mentioned, Dr. Miller, the fact that we had a higher dose, 10 times higher than the dose that we believe is the correct dose, gives us some comfort that a dose 10 times higher has been studied in many patients. So, that gives us more comfort than in many other trials.

DR. MILLER: Thank you.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: I was just curious about the necessity for pregnancy tests and two forms of birth control when your animal data indicated no

problems and you are dealing with a very elderly population. What was the necessity for this?

DR. ADAMIS: That is the miracle of modern medicine. There are people over age 50 having babies. It happens rarely but, you know, in this case one can't be overly cautious so that was the reason for that.

MS. KNUDSON: Two forms of birth control?

DR. ADAMIS: That is the standard protocol in clinical trials.

[Laughter]

MS. KNUDSON: Did you pay for them?

DR. ADAMIS: I don't know. I will find out.

[Laughter]

DR. DUNBAR: Are there any additional questions? Dr. Steidl?

DR. STEIDL: Thank you for a superb presentation. I think I understand some of the rationale behind the 15-letter vision loss, the primary endpoint. I understand the comparison to PDT. Most of my patients, when I say "you have

only lost two lines of vision; this is a success," you know, they are not too happy with that, nor to they agree with me.

I guess one of the things that I really wanted to know, there was, I guess as far as I could see, only one paragraph devoted to quality of life. Of course, if a patient has one bad eye they may notice more in the treated eye than if the other eye is 20/20, but I am just curious what your feelings are, your comfort is with this. As physicians, we often think it is good for the patient but, you know, in terms of the patient's perspective on this what have you gotten from your trial?

DR. ADAMIS: Sure. First, I would also mention that this difference, as we mentioned earlier, is against a usual care control and actually provides for approximately three-quarters of patients the only positive one-year data. So, we think that that is very, very important, in addition to the fact that the primary endpoint was supported by every secondary visual angiographic

endpoint that we saw. So, that gives us great confidence in our endpoint. Slide number Q-2, please.

[Slide]

We agree that it is very important to look at quality of life measurements, and we did using the NEI-VFQ25 which, as many of know, is a validated measure. It was only measured in one of the trials, in trial 1004 which was the North America trial. Because validated foreign language versions were not consistently available we did it in just the one trial. For that reason, we were significantly under-powered. We could not pool the data. The results were not statistically significant but there were trends that favored pegaptanib treatment. As I said, it was under-powered really to detect the small but potentially meaningful differences between groups. Slide Q-3.

[Slide]

We can see some of these differences. It is important to mention that a 5 or more difference

in the LS mean is considered potentially to be meaningful. So, anything between 0 and 5 is probably not meaningful. What you can see here are 5 data points that hit that 5 level for the 0.3 mg dose, and this has to do with color vision, peripheral vision, distance vision, social functioning and role limitations. So, these strong trends, despite a very under-powered sample, give us some confidence that the QOL, very much as the angiography and the other secondary visual endpoints, also supports the primary endpoint, and we are getting significant benefit for these patients, not, as you say, just measuring on an eye chart, but actually benefit that is important to them in the real world to help them get around.

DR. DUNBAR: Thank you very much. At this point we will take a 15-minute break and begin again at 10:30.

[Brief recess]

DR. DUNBAR: We will begin the agency presentation by Dr. Jennifer Harris.

FDA Presentation

DR. HARRIS: Good morning.

[Slide]

I am Dr. Harris and I was the primary medical reviewer for Macugen.

[Slide]

I am not going to repeat everything that the sponsor has presented to you; I am just going to try and bring up the salient points to try and give you an idea of how we went through the application and what we thought was important to present this morning.

I will go briefly over the study design; the efficacy results for each individual study so you can see what replicated itself and what did not replicate itself; conclusions about the efficacy; a safety overview of the combined study, the pooled study overview. There are a couple of specific safety concerns that we want to talk about a little bit more and the sponsor discussed a little bit this morning but we just wanted to go over those again. Then conclusions about the safety and then we are going to briefly go through the questions

that we are going to pose to the advisory committee and, of course, you will see them again after lunch.

[Slide]

Again, there were two Phase III studies, 1003 which was an international study, and 1004 that was done predominantly in North America.

[Slide]

Both trials were randomized, double-masked, sham-controlled as you have heard, dose-ranging, multicenter trials. Within the trials patients received intravitreous injections of either 0.3, mg, 1 mg or 3 mg every 6 weeks for 54 weeks. These trials were actually 2 years in duration. The data that we will be looking at today is only from the first year of the trial. At the 54-week time period these patients were re-randomized.

[Slide]

This is just a little schematic, just to show you where we are. We are at week 54 and this is the data that you will be seeing. The two-year

data is probably sometime soon I think, this month or next month. This is not the data you will see today.

[Slide]

Subjects that were enrolled in these trials were over the age of 50. They had subfoveal choroidal neovascularization secondary to AMD. The total lesion size was less than 12 disc areas, and greater than 50 percent of the lesions had to be active CNV. The best corrected visual acuity had to be between 20/40 and 20/320. These patients, as you have heard, were allowed to have PDT before entering into the trial and they were also allowed to have PDT during the trial. Prior to the trial they could not have had anymore than one prior photodynamic therapy treatment, and the patients could not have had any previous subfoveal laser treatment.

[Slide]

The primary efficacy endpoint, again, was a proportion of patients who lost less than 15 lines of visual acuity from baseline at 54 weeks.

Those are considered responders. Secondary efficacy endpoints were the proportion of patients gaining greater than 15 letters of vision, proportion of patients gaining more than zero letters of vision, and a mean change in visual acuity.

[Slide]

Just to give you an idea of the subject disposition, there are approximately 612 patients in the 1003 study that were randomized to treatment. Approximately 53 percent of these patients discontinued. As you can see, it was pretty well distributed. The treatment groups were consistent, with approximately 10 percent or so of patients discontinuing in each of the treatment groups.

[Slide]

For the second study, 1004, we see the same thing. The distribution of patients enrolled was approximately the same in each treatment group, including sham and, again approximately 10 percent or so of the patients discontinued therapy.

[Slide]

I am showing you this, not that I think that you can probably read it but just to give you an idea of who was enrolled and to show you really that the groups were well balanced. They were very well balanced between all three active treatment arms, including the sham. The demographics of patients that were enrolled in the 1003 trial were consistent with patients who actually had the disease.

I also wanted you to note down at the bottom that patients with all subtypes of neovascular AMD were enrolled. There was a substantial number of patients with predominantly classic and occult lesions that were enrolled in the trial.

[Slide]

The same thing can be seen for study 1004 where the groups, again, were well balanced, were representative of the population in which the disease was seen and, again, all three subtypes of neovascular AMD were represented.

[Slide]

Now I will go into the efficacy results. Before we go to the efficacy results I want to just put up this slide to show you how corrections were made in the p value. As we went into the Phase III trials we did not go into these trials with one optimal dose and, therefore, you know if you have one optimal dose, one time point, you look at the 0.05 value and you can determine whether the drug works or not. We went into the Phase III trials and we had three different doses so we had to find a way to correct for that. A decision was made to use the Hochberg procedure to actually control for these multiple comparisons.

With the Hochberg procedure, each of the treatment groups was compared to sham and if all three of the p values were less than 0.05, then we were considered to have three active doses. If not, if two of the p values were less than 0.025, then we had two active doses. Or, if one of the p values was less than 0.0167, then we had one active dose. If none of these criteria were met, then we

had no active doses. So, as you go through the results you may see some 0.05 or even 0.025 and that may or may not mean that that was actually statistically significant.

[Slide]

This is the primary efficacy result for study EOP1004. As you will see, at month 12 for the 0.3 mg dose there was approximately 67 percent treatment effect versus 53 percent of the sham group. This was a statistically significant result, with a p value of 0.016. Again, the actual treatment effect is about 14 percent over sham. The 1 mg group did show that there was a 67 percent treatment effect versus 53 in sham. However, this did not meet our pre-required p value.

[Slide]

For study 1003 we have similar results and, again, the 0.3 mg group shows approximately a 73 percent treatment effect versus 60 percent of sham, with a p value of 0.01. In this trial it was also seen that the 1 mg group was also statistically significant with a 75 percent

treatment effect versus 60 percent.

So, it appears that both the 0.3 mg and the 1 mg group have approximately a 15 percent treatment effect over sham, with the 0.3 mg replicating its results in both trials and the 1 mg dose did not replicate these results.

[Slide]

You have seen this graph before. This shows you what was happening to the patients' visual acuity in study 1004 throughout the first year of the study. What we see is that all patients continued to lose vision in all treatment groups, including sham, throughout the first year of the study. That being said, it does appear that the patients in the sham group lose vision at a higher rate than those in the other three active treatment groups.

[Slide]

In study 1003 we see the same thing. All patients continued to lose vision throughout the first year of study on active treatment and in sham, but those patients in the sham group appeared

to lose vision at a faster rate than those in the Macugen treatment group.

[Slide]

We have a chart similar to the sponsor's in that we looked at a subgroup analysis. The reason why we do that is to make sure there isn't one particular group that is actually driving the results. As we see in this chart for study 1004, if we look at all the subgroup analyses that were done, the type of AMD, color of the irises, the lesion size, baseline demographics and male/female, what we see is that for each subgroup analysis the 0.3 mg group shows a higher response rate than the sham group in each of the subgroups.

[Slide]

This was repeated in study 1003 where, again, the 0.3 mg group shows a higher response rate in all of the subgroup analyses over sham.

[Slide]

We also wanted to take a look at lesion size, basically because of the proposed mechanism of action of Macugen, and that is to inhibit

endothelial cell growth. So, we wanted to see whether that was, indeed, happening. What we noticed was that actually the total lesion size for patients, as well as the total size of the CNV and the total leak size, continues to increase for all treatment groups. Even in patients receiving Macugen, lesion size does increase but it does appear that it increases to a lesser degree in the 0.3 mg group than in sham. However, it is noted that it does increase in size.

[Slide]

The same thing was seen in the 1003 study where, again, the total lesion size for all treatment groups did increase in size, however, for the 0.03 mg group it does seem to increase to a lesser degree than in the sham group.

[Slide]

As you have heard, patients who entered the trial were allowed to get photodynamic therapy, which is an approved therapy for AMD. So, our question became were we really seeing an effect of Macugen or were we just really seeing the effect of

patients receiving an already approved therapy? So, we took a further look at this and the first chart you see here is the number of patients who actually got on-study photodynamic therapy treatment in study 1004. We see that approximately the same amount of patients actually received photodynamic therapy in all treatment groups, including sham.

Another thing that we did note is that while the protocol specified that only patients with predominantly classic should have been allowed to get photodynamic therapy, there were many people who had occult or minimally classic CNV who also received photodynamic therapy.

[Slide]

The same thing was seen in study 1003 where approximately the same amount of patients across the treatment groups received photodynamic therapy, with some occult patients and minimally classic patients, again, receiving photodynamic therapy. What was also interesting was that the 1003 study was an international study and you can

see that there were approximately half as many patients who received PDT in the international study versus the American study. That could be based on practice patterns across the ocean.

[Slide]

We also wanted to look at not so much what percentage of patients got photodynamic therapy but were more patients in one group or the other receiving more treatments? As we look at this chart for study 1004, we are looking at the total number of photodynamic therapy treatments. We see that there is substantially less number of treatments that were given in the 0.3 mg group versus that given in the sham group.

[Slide]

For study 1003 the results are similar. While there is not that big of a difference between wham and the 0.3 mg group, the point is that there were less photodynamic therapy treatments given in the 0.3 mg treated group.

[Slide]

Lastly, we wanted to look at the results

and say, well, it looks as though the same percentage of patients were receiving photodynamic therapy; it looks as though the same number of treatments were given. Well, did that make any difference in terms of the responder analysis, the primary efficacy endpoint?

So, what you are looking at here is the responder analysis at month 12 for four different groups, the first group being the group that received no photodynamic therapy either before the trial or during the trial. The second one are those patients who only received pre-study PDT. The third is a group that received on-study photodynamic therapy only. The fourth group are those patients who received pre-study and on-study photodynamic therapy. The last line here is for reference so you remember what the primary efficacy results were for all patients that we just looked at.

What we noted, which was good, is that the majority of the patients who entered the trial never had any confounding or problems with

photodynamic therapy, and that their results actually were pretty consistent with the overall results. In terms of the number of patients who received photodynamic therapy either before or during the trial, or both before and during the trial, those numbers were so small that we really can't make any conclusions about whether receiving photodynamic therapy before or during the trial has any effect on the efficacy results.

[Slide]

Similar results were seen for study 1003, where we looked at the number of patients who actually received photodynamic therapy. They are extremely small and no conclusions can be drawn from using concomitant PDT therapy. The results for those patients who received no photodynamic therapy, again, were consistent with the overall efficacy results.

[Slide]

We were curious, I mean, our primary efficacy endpoint is really those patients who lose less than 15 lines of vision. We know, based on

the disease process, that patients will continue to lose vision so those patients who lose less than 15 lines, that is probably a good thing for them. But we wanted to know was there any possibility that you could actually gain vision if you use this drug. So, we looked at the number of patients who gained greater than 15 letters of vision.

If you look at study 1004, actually there is a statistically significant increase in patients who actually gained vision in the 0.3 mg group and the 1 mg group as compared to sham. However, those results were not replicated in the 1003 study where you see no statistically significant gain in vision.

[Slide]

So, in terms of our efficacy conclusions, we believe that Macugen 0.3 mg does reduce the risk of vision loss in patients with neovascular age-related macular degeneration. But keep in mind that there is only approximately a 15 percent treatment effect over sham, and that there is no clinically meaningful increase in vision seen in

patients during the first year of using Macugen.

[Slide]

The sponsor has presented all of the safety results. I am not going to go back through all of them. I just want to say that we agree that similar events were seen in all treatment groups and no dose-dependent adverse events were seen. Most of the events, we think, were related to the act of giving an intraocular injection itself and no so much to the drug. The majority of adverse events, things like eye pain, superficial punctate keratitis, floaters, iritis are those things that we commonly seen with intraocular injections of any drug.

[Slide]

But there are two safety concerns that we want to talk about a little bit more. That is, endophthalmitis again and also a little bit about systemic VEGF inhibition and what that could mean.

[Slide]

In the database we had there were 16 cases of endophthalmitis. What we heard this morning is

that actually there are 2 more cases. I guess there is a total of 18 now. Of those 16 cases, all of those 16 cases occurred in the pegaptanib sodium treated patients, and none of the cases were in the sham treated patients. All 16 cases occurred within one week of injection.

[Slide]

So, I took a look at what kind of organisms were actually coming out of the endophthalmitis samples. We see that of the 16 cases, the overwhelming majority are those types of organisms that are commonly seen around the lid or around the ocular area--coagulase negative Staph., Staph. epi. There were about 6 cases that were actually negative on the samples. So, it stood to reason that maybe the problem was with the injection procedure and the sponsor did take a look at that and made some changes.

[Slide]

The original procedure called for the patients to get 2-3 drops of 50 percent saline diluted, 10 percent povidone-iodine or they could

receive 1 drop of topical antibiotic.

[Slide]

An amendment was made in the protocol after I think 12 cases of endophthalmitis, and it was changed so that patients would undergo a more sterile preparation procedure, similar to most intraocular surgeries, and patients would be prepped and draped similar to intraocular surgery and patients would receive either pre-injection topical antibiotics for 3 days prior to injection or 5 percent povidone-iodine flush immediately prior to injection.

[Slide]

So, what happened to the endophthalmitis cases? Well, we saw in the database that actually 13 of the 16 cases occurred before the protocol amendment. Three of those 16 cases occurred within 3 months after the protocol amendment. This is actually wrong now because I guess there have been 2 additional cases since that time. Based on the data that we had, there had not been any new cases of endophthalmitis 3 months after the protocol was

amended.

[Slide]

I just want to touch a little bit on systemic VEGF and what that could or could not mean in terms of this. Obviously, having VEGF is a good thing in some instances and it is a bad thing. It is a bad thing in the eye. We want to inhibit that in cases like AMD. But we want it in the systemic circulation, mainly because it plays an active role in cardiac angiogenesis. This is important in collateral blood vessel formation in patients with myocardial ischemia. It is also an important vasodilator and it helps to maintain coronary artery blood flow and helps maintain patency of coronary arteries.

[Slide]

So, what we did is we looked at the whole database and we said, well, are there any events within the database, the adverse event database, that could possibly in any way be related to VEGF being inhibited in the systemic circulation?

Of all the things that we came up with--

arrhythmia; atrial fibrillation which could be an early indication of myocardial ischemia; bradycardia; chest pain; coronary artery disease, not just those cases where patients obviously came into the study with a known diagnosis but those patients who were diagnosed with coronary artery disease during the trial; and myocardial infarction--and we looked at the database and said, well, is there a problem? Could we actually have these systemic anti-VEGF effects based on the intravitreal injections? What you see here on the chart is that actually all the numbers are pretty small across all the groups, and there is no real indication that the intravitreal injection of pegaptanib will have any systemic anti-VEGF effects.

[Slide]

Just for completeness, in terms of the death rate, there were approximately 25 patients who did die during the study, approximately the same in each study, and the majority of causes were actually things like cardiovascular events,

malignancies and they were pretty typical of the age of the population that we were studying. So, we think those events were really due to the population and not actually to the drug.

[Slide]

In terms of safety, similar events were seen in all treatment groups. The most frequently occurring adverse events related to the intraocular injection itself and not to the drug. The risk of endophthalmitis appears--and I have to emphasize "appears" since there may be more cases that we haven't seen--to be minimized by sterile technique and there does not appear to be an apparent increase in the risk associated with systemic anti-VEGF activity.

[Slide]

We will just go over the questions briefly. You are going to see the questions again this afternoon but just so you can start thinking about them. The questions that we would like to have discussion about are, one, based on the inclusion and exclusion criteria, are there

patients excluded from the studies that you believe need to be studied?

Visual acuity measurements were conducted using the ETDRS scale at 2 meters. The validity of the ETDRS scale was established based on ratings at 4 meters. Are the visual acuity findings sufficiently robust to overcome the potential bias introduced by visual acuity measurements taken at 2 meters?

[Slide]

Has sufficient data been submitted to evaluate the efficacy and safety profile of pegaptanib sodium for the treatment of the neovascular form of AMD? If not, what additional data are needed?

Are additional analyses of the current data needed to understand the efficacy or safety of pegaptanib sodium for the treatment of the neovascular form of AMD?

Has the concomitant use of PDT therapy with pegaptanib been explored sufficiently? Are there concerns with using this predictive

concomitantly with PDT?

[Slide]

Do the route and/or frequency of administration of the drug raise any concerns that are not addressed by the studies?

Endophthalmitis was observed in approximately 2 percent of patients in the studies. What is the optimal follow-up needed to minimize the impact of potential endophthalmitis cases?

Are there any other adverse experiences that are of particular concern for this product?

VEGF has been shown to be an important component in the development of collateral vessels in ischemic heart disease. Inhibition of VEGF in the systemic circulation could present a theoretical increased risk of symptomatic cardiovascular disease in the target population of elderly patients with AMD. Has the adverse event profile of the two randomized Phase III trials raised any concern over the possible systemic effects of this therapy? Is there additional monitoring that should be in place for patients on

pegaptanib sodium therapy? Thank you.

Committee Discussion

DR. DUNBAR: At this point I would like to open the floor for questions for either the agency or for the company. Dr. Pulido?

DR. PULIDO: Thank you. Two questions, the first one is you said the treatment effect was 15 percent. That is because you took the 67 minus 50. Again, I am not a statistician; I am a clinician--shouldn't it be the difference divided by 50 to give you 25 percent as the treatment effect? So, the delta of 15 over the baseline which is 50?

DR. CHAMBERS: There are obviously lots of different ways to look at it. What we have been doing for ease of description is just to describe what the percentage difference is between the two different modes of therapy, and we thought that easiest to be described as just a 15 percent difference in the percentage of people who have lost 3 lines of vision.

DR. PULIDO: The other question I had, and

maybe it would be better answered by the company, when one looks at the serum levels, is that the total amount of the drug that is being measured or is that the unbound free form that is being measured?

DR. ADAMIS: It is the total level.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: Are there known levels for VEGF or VEGF inhibition that are clinically significant from the cardiovascular current literature?

DR. ADAMIS: The short answer is no in humans. The longer answer is that the most sensitive signal of systemic VEGF inhibition is hypertension. In the Avastin trials they picked it up in their colon cancer, the renal study, their lung cancer study, and some of those were much smaller studies than ours and there was no evidence of hypertension as a function of use of pegaptanib in our study. So, I guess whatever that level is--and it hasn't been determined--we are probably well below that.

DR. DUNBAR: I have a question for the agency about the duration of use of the drug. I would like to know who will decide when to stop therapy, the agency, the sponsor, or the patient's physician? Is this something that will be specified by the agency in relationship to the drug approval process? Would it be included in the labeling? Or, is this something that we won't know for many years and would be addressed in further labeling decisions?

DR. CHAMBERS: The most accurate answer is that I think we will not know for a number of years. The answer that everybody would like to know is probably best studied by a 10-15-year study of giving a particular product. We obviously run into the difficulty of not having a therapy that is potentially valuable available during the time that we are doing that so we have chosen to take a path where, if everything else looks good--and I will repeat that decisions have not been made on this particular product and there are lots of other parameters that still need to be reviewed, but if

this product otherwise looks fine we would potentially label it based on the information we have available.

As you have heard, the sponsor presented that as of their latest data safety monitoring committee they have 90-some odd percent of the information for the two years. To the extent that we have two-year data, we will list two-year data. If we don't, we will list one-year data and as more data becomes available we intend to amend the label to reflect what we know.

DR. BULL: I have one thing to add to that. There is the opportunity for the committee to make recommendations if you are uncomfortable with the degree of follow-up, things such as Phase IV commitments. I mean, there are a number of options that can be systematically required of the sponsor to do to look at the long term.

DR. GUYER: I think in answer to your question, also clinical judgment of the ophthalmologist will decide much of it until, as Dr. Chambers mentioned, we do have the answer from

continuation of trials. If a physician sees a patient that is, for example, scarred down and realizes there is no further benefit of treatment, we would expect that the physician would stop that treatment, whenever that is and. Similarly, if the physician sees active bleeding going on they might continue it. So, I think a lot of it will be in the clinical ophthalmologist's hands, at least in the beginning.

DR. DUNBAR: That was my concern, that a patient with a quiescent, scarred lesion was vulnerable, worried about their blindness and might subject themselves to very frequent injections for a long period of time. Dr. Lehmer?

DR. LEHMER: We are certainly in the era of implantable sustained release drug delivery devices. At what point time-wise, if therapy is determined to need to continue past a year or past two years, should a recommendation for conversion of this drug to an implantable device become necessary?

DR. ADAMIS: It is an area that we are

very interested in, in the laboratory of the sponsor. So, we are working on alternative formulations to see if we can get an extended release profile in implantables of that sort. I think ultimately that may end up being an improvement.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: I just don't seem to understand why the DSMB permitted the trial to continue with the sham arm when at every point it appears the sham arm is inferior to every drug dose that was given. This is a disease, as I understand it, which continually advances and one should treat patients.

DR. ADAMIS: Yes, the data safety and monitoring committee, their charge was to monitor for safety. But the point you raise is a very important one. So, in this randomized, discontinuation trial design we actually allow people who discontinue the drug and lose two lines of vision to go back on so patients are not forced, by and large except for a very small group, to stay

on sham for two years.

DR. DUNBAR: I have a question for Dr. D'Amico. I was interested in Dr. Harris' presentation that 6/16 endophthalmitis patients had sterile endophthalmitis. I wonder, with your experience with endophthalmitis, if you could tell us do you think that these patients had infectious endophthalmitis that were culture negative, or do you think that that may be more of inflammatory response?

DR. D'AMICO: Yes, in the trial, looking for both of those things, that is inflammation after injection or specifically infections, we found really no evidence of a widespread inflammatory effect at all. In studies of endophthalmitis in general, for example after cataract or other forms of ocular surgery, invariably large studies always find that approximately two-thirds will be culture positive and one-third are, inexplicably, culture negative. Now, what are those one-third? Well, some of them will be organisms that have just not been

successfully collected by the culture technique. Perhaps the specimen was too small; perhaps the laboratory didn't plate it properly, or something of that nature. Some of them may be fastidious organisms that are difficult to culture. But clinically I think we treat those cases as presumed infectious. The patients had acute presentations and they were invariably managed with TAP and antibiotic injection. So, I think that they mirror my clinical experience with endophthalmitis cases, except somewhat for their outcomes which were surprisingly somewhat better. They suggested somewhat better visual outcomes than we might see in clinical cases that, for example, would occur in another context, after cataract or something like that. Have I answered your question?

DR. DUNBAR: Thank you. Dr. Gates?

DR. GATES: Any conclusions as to that? Is it a smaller bacterial load perhaps with this injection?

DR. D'AMICO: Well, it is a new phenomenon. Certainly, these patients were

extremely well followed and they included, you know, contact with the patient and education to inform patients about side effects, etc. So, the patients were promptly detected, but it could be that the load that is introduced in an intravitreal injection is lower and, consequently, it has a less fulminating presentation, but I don't know.

I will raise it because someone will, it also may be that there is some interaction between a VEGF medication and a profound inflammatory infection in an eye. But that remains completely speculative but it is something interesting, as a scientific point of view, for further research.

DR. ADAMIS: Just to follow on Dr. D'Amico's comments, there are data in the laboratory now that VEGF can be pro-inflammatory, and in models of ocular inflammation VEGF levels come up and it is associated with the vitritis and flare, and we have published, and others have, that if you block VEGF in that sort of instance you can decrease the inflammation as well as the leak. So, it is speculation, as Dr. D'Amico said, but it is a

plausible hypothesis that it may be having somewhat of an anti-inflammatory effect as well and you get less standard damage that occurs when neutrophils rush in in a case of endophthalmitis, but it is a theory.

DR. DUNBAR: Dr. Chinchilli?

DR. CHINCHILLI: Yes, I have a question for the agency. In the briefing document you showed the results from the worst-case analyses. I notice that in your presentation you really didn't discuss that. Is there a reason you didn't present them today? I mean, how do you feel about--well, I will tell you that I think you shouldn't do them but I was wondering why you didn't present them but they are in the briefing document, or am I reading too much into that?

DR. CHAMBERS: We do a large number of analyses, which are neither shown in the briefing document nor shown in the presentation, to try to look at the robustness of the findings. We thought it instructive to give what potentially is a bottom lower limit and include it in the briefing document

just to try and frame people's idea of what the magnitude could be of inclusion or exclusion of different findings, but since it does not necessarily represent an accurate finding we didn't think, from a time perspective, that it was worth continuing to present in a presentation.

DR. CHINCHILLI: Well, I think it is highly inaccurate. I know you try to look at the bounds but I think they are highly inaccurate bounds. Later today--I don't know if you want to get into this now, but I do have some recommendations about analyses, endpoints and things like that. So, I don't have to get into that now.

DR. CHAMBERS: We don't disagree with you. We don't think either of the analyses are necessarily the most accurate; we could do something in between.

DR. DUNBAR: Is there additional discussion for the agency presentation at this point in time?

[No response]

Now we have a decision about our agenda because we have significantly more time with our morning session than we expected. It is imperative that we start the open public hearing as it is scheduled at 1:00 p.m. so that the public can have their voice in this matter. We have two options. One is that we can take a longer lunch period and then start the agenda for the afternoon as previously published. Or, we can begin to answer some of the FDA questions now and start our lunch closer to the scheduled time and then have the public hearing at 1:00 p.m.

So, let's begin to answer some of the FDA questions now and then we will, of course, begin the public hearing at 1:00 p.m.

DR. CHAMBERS: We would like to hear some general discussion as opposed to just going through the questions. So, that may be a better use of some of the time this morning, just a general discussion of the different topics that are on there and then specifically go through questions later.

DR. DUNBAR: Then we will start with Dr. Chinchilli in terms of general discussion from the committee.

DR. CHINCHILLI: Well, I mentioned this in my previous question and I would like to talk about the endpoint that is used and the analysis. I don't quite understand why the analysis was done this way, and then looking at the briefing documents I see that this is the way the FDA recommends the analysis be done. But there is interest in less than 15-letter loss. I think it would be better to reverse the definition, to look at someone who fails, someone who is a treatment failure who has 15 or more letter loss and then look at the time to occurrence of that event. This way you would better handle the dropouts and the censoring that occurs.

Now, I realize the subjects in these particular studies come into the study every six weeks so you don't have a nice continuum for determining when this treatment failure takes place, but at least you can have more of a discrete

failure time process. It would just get away from looking at these extreme cases, the worst-case scenario that the agency likes to look at in terms of bounding the results. It just seems to me that that would be a better approach to the analysis, that is, to reverse the definition and talk about treatment failure and look at time until treatment failure occurs, and doing time to event analyses. That would be a much more accurate analysis, I feel. I don't know how the agency feels about that or if they would consider that. I don't know if there is some reason I am missing that that is not a good approach. And, maybe the company would like to comment on that as well.

DR. CHAMBERS: We are certainly open to looking at a number of different types of analyses and different ways of doing it. The general recording of visual acuities has been every three months, not every six weeks. Consequently, you have set fixed time points when you are getting the information. So, time to event, when you are fixed at every three months, we have not thought as being

particularly meaningful.

Whether you look at it on either side of this coin, whether it be the people that improve or the people that fail, we have generally thought as being relatively similar. There are certain biases that go in as far as the dropouts and which way they are treated. Obviously, if you are assuming that somebody is going to drop out and they never get seen again, they don't get counted as a loss. That accounts for some of the reason for doing a number of the analyses that we do.

But, as I said, we do a large number of different analyses looking at these things to try and look for the robustness of the findings. In this particular case, any way you look at it you have very similar results. So, we did not stress how it needed to be presented for this particular case.

DR. CHINCHILLI: I agree. I mean, the dropouts in these two trials was between 10-12 percent so that is not extreme. But I think you are going to have trials where you may see more

dropouts, a higher rate than that, and all these cases that you are proposing for analysis all involve some form of data imputation. If you look at the treatment failure approach and time to event analysis, you know, you account for that censoring and you are not imputing data the way you do in the current methods. You know, I think I am getting off the tangent here, but it just doesn't sit well with me the way the outcome is constructed and all these analyses are performed that involve some form of data imputation. Again, I agree. I don't think it makes a bit of difference with these two particular trials here but in general it is not really good methodology.

DR. CHAMBERS: We certainly are interested in additional comments you have along that, although I am not aware of any method that doesn't have some type of bias and some type of assumptions in the way it is presented, including the methods you are discussing.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I just want to make sure I

understand correctly that, with regard to the analyses, the intent-to-treat is what has been presented, being the most inclusive; the per-protocol analysis being the most exclusive. As I understand from the briefing, when the two were compared there were no significant differences and, therefore, that is why we are using the intent-to-treat because we want to be as inclusive as possible to get the safety data. Is that a correct interpretation of why we are using the intent-to-treat analysis?

DR. ADAMIS: The safety data population is even a little bit larger. Everybody was randomized and received one treatment. The intent-to-treat was the folks who had one baseline vision as well.

DR. GUYER: Can I have slide E-101, please? Maybe we can just summarize this.

[Slide]

This shows the definition of the various populations that we looked at, and it shows that the all-randomized group were those that received an actual randomization number. In this case it

was 1,208 and that represents the largest number--as you said, one extreme. The safety group received study drug, and that was 1,190, slightly fewer. The intent-to-treat were patients, by the sponsor's definition, that received study drug and had an observed baseline vision. That was 1,186. The per-protocol was all of the ITT patients that had an observed post-baseline vision and no major protocol violation. So, as you mentioned, it is a much smaller group because they observed the protocol perfectly and also had an observed time point at week 54. That brings you down to 1,144. Then you have a week 54 observed which are the actual patients who received the study drug and had a baseline vision and also a week 54 vision, and that is 1,085.

[Slide]

Just to illustrate further maybe some of the differences, E-102 shows again, starting with the all-randomized where you start with 100 percent of your population, going down to week 54 where you get 92 percent of the data, at least for the 0.3

mg.

[Slide]

Finally, if we go to slide E-103, this again shows just the two extremes, so to speak, the all-randomized with an LOCF, which is in the FDA briefing book, and the intent-to-treat where study medication and baseline visual acuity occurred, which is in our briefing book. Very importantly, you can see that they are all the same. Slide E-113.

[Slide]

We can see that on the left we have the ITT population using an LOCF, which is in the sponsor's briefing book, and we have the all-randomized LOCF when there is a true ITT, in the FDA briefing book. Then we have some of the extremes, the per-protocol observed and the week 54 observed. Then you can see that we have very robust data and that the sensitivity analysis and different analyses all show, for the 0.3 mg dose, a statistically significant change. So, any way you look at it, either extreme, we see robustness of

the data.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Ms. Chairwoman, your question had been do we have general comments at this point, and I would just like to state that I think the data at this point looks very favorable. I would say that my concerns about systemic complications, from the data, appear very small.

My only concern is the long-term use and the fact that there is the second aspect of VEGF that only recently we are learning about, and I would like to see some long-term follow-up using ERGs and possibly visual fields in a small group of these patients to make sure that there are no long-term consequences of long-term use of this drug. Otherwise, I am very impressed.

DR. DUNBAR: Are there any other general comments from committee members? Dr. Steidl?

DR. STEIDL: You can correct my thinking if I am wrong here, but it looked as though the lesions continued in general to grow, maybe at a slower rate, in the treated group. With the

half-life of, I guess, about four days and effective vitreous concentrations that are weeks, it would seem with that trend that it is quite possible that this may be needed for a while beyond the study time period. You know, somebody mentioned the 0.16 percent per injection in endophthalmitis rate. If you multiply that times nine it gets pretty close to what was seen. I don't know if it is valid to extrapolate that, but then if you start thinking about doubling the time and getting maybe to 3-4 percent, from my point of view, it is getting pretty scary.

I don't tend to view those, from a retina point of view, as sterile endophthalmitis because in our lab we get a third to a half of clearly infectious cases that don't come back positive. I am wondering if that seems like a logical assumption, that if this is to carry on we could assume that the endophthalmitis rate would grow proportionally.

DR. ADAMIS: Yes, I think your interpretation of the data is correct and,

obviously, the cumulative risk increases as a function of time. What our goal is, and we take this responsibility seriously, is to make sure that the injection procedure, which may be a modifiable risk--that the risk gets down as low as possible. We were fortunate in the second year after the amendment to actually see that rate go down and, subsequent to the amendment that occurred last May, it is down to 0.03 percent per injection.

The other aspect of it that is equally important is the visual outcome. That is, if this event happens, are these patients being diagnosed rapidly and being treated appropriately, and then doing everything you can to preserve the vision as a function of getting the infection. I think our investigators did a rather superb job in the sense that everybody was diagnosed within a week. Everybody got intravitreal antibiotics. Over half of them had vitrectomies and you saw the visual outcomes. I will tell you that the visual outcomes in the second year with the additional cases are the same, if not better, than what you saw in the

data presented today. But your thesis is correct that the more you use the drug, there obviously is an incremental risk over time that increases.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: So, yes, there is a risk of using intravitreal injections, but the alternative is the present forms of treatment or systemic medication that also increase the risk. It is a small risk but I would rather take that risk than give something that has systemic effects.

DR. ADAMIS: A point well taken. As Dr. D'Amico said, I mean, it is important to take it in the context of the potential benefit. So, the reduction in severe vision loss is greater than 50 percent and the severe vision loss we saw as a function of endophthalmitis was 0.1 percent. On balance, at least in this first year, it looks like the benefit outweighs the risk.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I agree with Dr. Pulido. The data are very impressive. Along the lines of what should be looked at in the future--the PDT impact.

Obviously, we are not able to really assess that based on the numbers, but taking this information forward, seeing what are the clinicians going to do with this data, in other words, who do we apply PDT to, what kind of population--a patient comes in with macular degeneration, do we use Macugen? Do we use PDT? Do we use both?

I suppose if patient recruitment were going to start now we would see a much larger percentage of the European community using PDT since it has been approved there and there has been some expanded use of PDT. So, I guess as far as a future analysis--I don't know if that is already under way--I would like to see more data on the impact of PDT.

DR. GUYER: I think that is a very important point. One of the things that was important to us when we designed this trial was to try to make it as much of a real-world trial as possible. That is why we allowed photodynamic therapy in it. Showing the data, we can't say a lot about combination use or anything like that,

but I agree with you that certainly future trials will be able to address those issues and it is important.

DR. DUNBAR: Mr. Kresel?

MR. KRESEL: I guess being the pragmatic industry representative, I will ask the question the way I look at things, which is that we had a lot of discussion about endophthalmitis and I think you gave a really good answer as far as how the patients were treated and how they were followed up. But they were in a clinical trial where, you know, they came back to see the physician at these intervals. So, would you recommend in labeling that kind of a follow-up so that those patients are tracked and, in fact, appropriately diagnosed and treated?

DR. ADAMIS: The optimal follow-up I think still remains to be determined. One of the things we have done is we have given grants to specialists who are experts in this area to try to come up with a preferred practice recommendation. The only thing we can say is what we did and what the

results were. I think it is still an open question as to which variables that we changed, and we changed multiple and, as I said, the steroid injections were taking place at the same time in another population--which of those factors is the most important still remains to be determined and I think a lot more work needs to be done in that area.

So as regards to what we will recommend, it is still being decided. Until we hear back from the experts we obviously will tell people what we have been doing and the results that were associated with that.

DR. GUYER: I also want to comment--many of the retina people in the room know this--but in the last three or four years there has been a tremendous experience in the retinal world with the use of off-label intravitreal steroids because there is such an unmet medical need not only for this disease, macular degeneration, but also for diabetic macular edema. So, I actually think there was a tremendous learning curve for retinal

physicians learning the best way to do intravitreal injections. That occurred. We talked about the protocol amendment and we hope that that had some effect. But I think also equally important may be that the retinal doctors had a very, very good experience of the best way to practice intravitreal injection administration.

As Tony mentioned, we did sponsor a roundtable to try to get the thought leaders together on the best way, and Dr. D'Amico was at that and maybe he would like to comment on a few of the findings from that that could help guide us.

DR. D'AMICO: Yes, under an educational grant a roundtable was convened to look at the growing use of intravitreal injections in ophthalmic practice, and to try to assemble the best available information on what we know about how to make this procedure as safe as possible. In this roundtable there were experts from the point of view of infectious disease, from the point of view of vitreal-retinal surgeons, people who deal with antibiotic levels within the eye, and also

substantial representatives across industry who have pharmaceuticals that are used by intravitreal injection. While all I can tell you is that an article is in preparation that will be ultimately submitted to peer review literature, we have initial plans to submit that article to the journal Retina. It includes things such as the premise of using povidone-iodine which emerged as an incredibly important central aspect of using a lid speculum. We were finding that, in many casual surveys, people would do injections and allow the lid margins, etc. to contaminate the needle, and probably most importantly, to treat this as a sterile intraocular procedure.

I was present. I was asked to be a part of that committee and, if you wish, I have details about who was there, etc. But I feel that this document will be very valuable in helping the evolution of the understanding of intravitreal technique. So, it will become something that I think we can go forward with. We can look at various modifications now to make this safer and

safer.

But having participated in both the data safety committee and also this panel, I am quite convinced that the protocol modifications had a very real effect on reducing the incidence of endophthalmitis, and I am confident that incidence can be kept low and probably be even further reduced with appropriate education of both patients and physicians, as well as appropriate training.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Dr. D'Amico, there was a recent article I believe in The American Journal of Ophthalmology. It included people from Baskin Palmer, looking at the incidence of endophthalmitis following intravitreal triamcinolone injections, and the incidence was double that of this, wasn't it?

DR. D'AMICO: Correct. You know, it could never have been known when these trials were begun, but intravitreal injections have become quite commonplace in retinal practice now with off-label use of triamcinolone and the incidence which has

been reviewed shows that it is substantially higher. Although I believe that that incidence, in fairness, is decreasing as physicians treat the injection technique with additional seriousness and care. But, actually, a detailed review has been made available to this review committee and showed that the rate of endophthalmitis following intravitreal injection with pegaptanib was well within the range, and at the low end of the range, for intravitreal medication administration across the board.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: The only thing that confuses me a little is that you say that no patients receiving the sham treatment had endophthalmitis. Doesn't it seem that it is the drug then that was causing it?

DR. D'AMICO: Well, the sham patients did not receive the penetration of the eye with the needle so that explains why it is that event which, presumably, allows bacteria to gain entry into the eye.

DR. DUNBAR: Recently several of the comments reflected not so much concerns about the statistical significance of the efficacy of the drug but, rather, concerns for the future. Previously Dr. Bull mentioned that the committee can make Phase IV recommendations for plans for the future, for future studies. What is the mechanism for this? And, perhaps this is an appropriate time for the committee to discuss some of these future concerns.

DR. BULL: That would fundamentally fall under recommendations for additional studies. If these are data deficiencies that you might see as impacting marketing of the product, it would argue against whether or not you feel the data is sufficient at this point in terms of the efficacy assessment. If these are data needs that need to be obtained in a systematic way, they can certainly not hold up marketing of the product if you feel there is sufficient efficacy in terms of what you have seen.

We realize this is an incomplete data set

and I think that that needs to be kept in mind, given the earliness of where we are in this submission. In fact, there are modules in the NDA that have not come in and have not been vetted by the agency yet. So, I have to say that, you know, we haven't seen the data, as has been mentioned, in terms of the re-randomization. There are a number of sort of outstanding assessments here that I think certainly have significant implications for further work. But I think things that need to be looked at systematically certainly have the potential of being addressed in Phase IV.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Just for clarification, that could be a postmarketing surveillance. For instance, study ERG could be postmarketing, following marketing approval surveillance in that regard.

DR. BULL: You mean is post-approval?

DR. PULIDO: Yes.

DR. BULL: Potentially but, again, as I said there is a huge caveat here that we are still

very early in the review of this application and there are a number of other aspects, particularly from chemistry manufacturing issues, that will need to be addressed and other things that will impact the totality of our assessment of the data.

DR. DUNBAR: Dr. Chambers and then Mr. Kresel.

DR. CHAMBERS: Let me just clarify, the range of different options includes additional Phase III trials, additional Phase IV clinical trials, as well as postmarketing commitments, postmarketing monitoring. There is going to be a certain amount of postmarketing monitoring that automatically goes with any new drug product. But what you are describing would probably more accurately be done as actual controlled clinical trials because you want, obviously, a baseline as well as continued follow-up in order to look for any potential changes. That is probably better done with a control group and making sure you have everybody in your trial.

DR. DUNBAR: Mr. Kresel?

MR. KRESEL: I guess my question isn't really a question--well, it is but it is for the rest of the committee because it is not one for me to decide. But if I were in the sponsor's shoes, and I have heard people commenting on how long can we use this drug and what are the consequences, I guess I would like to hear the committee weigh in on how much follow-up post-approval the committee thinks is appropriate, for planning purposes. That is, you know, the sponsor is going to have two years of data pretty soon. How much data does the rest of the committee think is appropriate to continue follow-up?

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Trying to answer your question and Dr. Chambers' at the same time, I don't know whether it is necessary to do a randomized, controlled trial for the results of ERG. One possibility is that there hasn't been any change whatsoever so that if you take the patients that already have been in the trial for a year and do ERGs in a small group of them and compare it

even to the fellow eye and there is no difference, well, that tells you volumes. That decreases the chances of having to go ahead and do another randomized, controlled trial and slow the acceptance of this drug into the marketplace.

DR. DUNBAR: Dr. Chambers?

DR. CHAMBERS: Let me just ask don't you think there is likely to be decreased ERG in patients that had macular degeneration compared to the other eye?

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Not necessarily because macular degeneration is such a localized area that is involved that the ERG overall may not be affected. We know that macular disease does not affect a large part of the ERG. So, my only concern, again, is, is this affecting a broader area of the retina than what we are measuring by doing visual acuity measurements? If that is not the case, I don't think we should delay it.

DR. CHAMBERS: I don't know that we are talking necessarily about delaying it, but I guess

the question still in my mind is interpretation. If you don't see anything, yes, that is great. If you do see something, is that necessarily the drug product or is that the disease going on? And you don't know the answer to that.

DR. PULIDO: Then you would have to do the trial you were considering.

DR. DUNBAR: Taking a step back to Mr. Kresel's question, I would like to ask the other committee members if there is any sense among the committee to build a consensus of how long the company should study the drug for the future after this they finish this planned two-year period. Not so much requesting additional data such as the visual field and ERG that Dr. Pulido mentioned, but just to continue the clinical trial, is there any sense among the committee? Dr. Lehmer?

DR. LEHMER: In the PDT studies there was a physical endpoint of no leakage. Is there a similar endpoint with regard to this study looking for that type of endpoint or stabilization of vision? I think we have to have some kind of

clinically meaningful endpoint on which to base the answer to that question of how long do we carry the study for and, therefore, how long do clinicians expect to carry on the treatment.

DR. GUYER: In the photodynamic studies there was continued leakage. When they decided to retreat they would do a fluorescein angiogram to determine that. But over the course of the year, similar to what we have seen, there was still leakage occurring and that us the disease, and Tony can perhaps give us some hypothesis for why.

So, for that reason, I think the two-year data will be very, very important in the sense that we will learn more about two years of therapy versus one year of therapy. Until that data, as we mentioned earlier, I think what is nice about the eye is that you can look in and see the disease and a patient who has significant disease with large, scarred, poor vision obviously wouldn't be necessarily a good candidate to continue treatment. Someone that might not have any leakage, as you say, could be used as a clinical endpoint for

perhaps stopping treatment, and people who are actively bleeding would continue.

But it is important to say that really the only recommendation we can make is this clinically important finding is based on one year or 54 weeks of treatment. So, we really can't say anything more and it would be dangerous to try to speculate that less treatment could give the same effects. So, we believe that clinical judgment would be very, very important in determining long-term treatment.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: The other thing that I think is important is the fact that even with one-year follow-up--what was the mortality rate in this group of patients? Wasn't it 10 percent or something?

DR. ADAMIS: It was two percent in treated and sham alike.

DR. PULIDO: Right, so I mean you are already getting to a point where there is a certain mortality in these elderly patients. To continue

it more than two years, I think you are going to find a higher mortality rate and I don't know whether we are going to find more than what we are already finding.

DR. DUNBAR: Is there any additional discussion at this time? If not, at this point let's break for lunch and we will reconvene at 1:00 p.m. for the public discussion.

[Whereupon, at 11:45 a.m., the proceedings were adjourned for lunch, to resume at 1:00 p.m.]

A F T E R N O N P R O C E E D I N G S

Open Public Hearing

DR. DUNBAR: We are beginning the afternoon session of the Dermatologic and Ophthalmic Drugs Advisory Committee on Macugen with an open public hearing.

Both the Food and Drug Administration, the FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsors of any products in the pharmaceutical category under discussion at today's meeting. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in

connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

At this point of the open public hearing, I will ask speaker number one to please come to the podium. Each speaker will have seven minutes to present.

MR. GARRETT: Hi. My name is Dan Garrett and I am with Prevent Blindness America. My organization paid for my own travel to come here today and I personally do not have a financial relationship with any of the companies pertaining to this drug.

I mentioned I am with Prevent Blindness America. We are the second oldest voluntary health agency in the country. We represent organizations throughout the country that primarily focus their efforts on screening, training, advocating,

researching and educating people on the importance of good vision care. We also advocate for increased research funding and increased funding to the Centers for Disease Control in Washington, and we try to impact public policy as it relates to saving sight and vision loss.

The reason I am here today is not to endorse this product but to encourage the committee to make the right decision as it relates to the science behind this drug. It might suggest that this could prevent further vision loss for people with AMD. That is why I am here today. My organization does not endorse the product of discussion today.

A few thoughts and figures, and I wasn't here earlier today so forgive me if these are repetitive. It is important to point out that nearly 1.7 million Americans aged 40 and older have AMD, and if nothing is done by the year 2030 the number of blind and visually impaired could possibly double. So, we are talking about a fairly significant population. It is very important that

this committee consider this drug because it has the potential to potentially stop vision loss. Unfortunately, there is not a miracle drug out there yet that prevents AMD but, hopefully, with all the science and research that is going on that will be in the near future for us.

Another interesting statistic, and this could particularly hold for people with AMD because they are the ones that have most low vision, vision impairment is the cause of 18 percent of hip fractures, and most people that have AMD are living on their own and they have lost their central vision so it is very difficult for them to navigate their way around their home. If only one in five of those hip fractures were prevented, more than 440 million dollars could be saved annually so that is significant. So, any type of AMD drug that could prevent further vision loss is certainly a welcomed addition to the marketplace for patients.

My organization, again, advocates advancements in treatment of AMD, and I just want to say to the committee that I am sure you will

make the right decision on behalf of all the older Americans in this country for the people that have AMD. Anything that can prevent further vision loss should be welcomed. That is all I have to say. Thank you.

DR. DUNBAR: Thank you. At this point I will ask speaker number two to come to the podium.

MS. HOFSTADTER: Good afternoon. I am Ellen and I am 81 years old. I do not have any financial ties with the drug company except my stay in the hotel and my travel.

I was diagnosed with AMD two years ago. I belong to an HMO. The HMO doctors checked me and told me "you can go home; there's nothing we can do for you." But I didn't take no for an answer. I called the Jewish Eye Clinic and asked if there was a doctor who could see me. The girl says, yes, and in two weeks I have an appointment. I got Dr. Schwartz. I had an eye test, an angiogram and he looked my eye over and he said, "don't drive, but do not sell your car because we might can help you."

So, I took some lasers, some Visudyne in my left eye but it didn't help. So, my left eye is legally blind. Then I was approached by Dr. Gonzalez who asked me if I would like to step into a clinical trial with Macugen shots. Well, it was very heavy for me because when I was a young girl I was sent to Auschwitz and I was experimented on by the infamous Dr. Mengele. So, I had really a choice to make.

I didn't think long about it and I thought I want my sight. So, I told them I would. So, I got into the clinical trial and I got a Macugen shot in my right eye. It sounds very scary but really 20 minutes of discomfort is a small price to pay. After the third shot I gained my sight back to 20/20 and could read seven lines below. I had altogether 12 shots and three weeks ago I had my lost one and my sight is 20/20 in one eye.

And I really want to thank the researchers who worked so hard to find a drug like Macugen to help us for this dreadful disease. Thank you.

DR. DUNBAR: Thank you. Next I will ask

speaker number three to come to the podium.

MR. STEVENSON: My name is Nick Stevenson. I am the president of the Association for Macular Diseases. It is the only national support group that is solely concerned with both the practical and the emotional problems confronted by individuals and families endeavoring to cope with our particular type of eye disorder. To do that, we publish a newsletter which advises our members what is going on in the world of research, what is not. There is an increasing number of scams and frauds which are proliferating now not only in numbers but in funding as well, and we maintain a members hotline where members can always call in and we can act as a link between them, their problems and the problems that they may face.

I, myself, have been legally blind from the wet type of macular degeneration for 26 years. I have no financial interest in this pharmaceutical company or actually any, except that they did pay my travel and expenses to come down here. But what I would like very much to emphasize for all of you

is something that many of you, I can understand, have already experienced, how difficult and understandably difficult it is for a fully-sighted person to fully appreciate the enormous subtraction from life that loss of vision represents, for some far more than for others but, nonetheless, it is not something that any of us foresaw in earlier years of our lives. We may have thought of disasters overtaking us, such as being struck by an automobile or some disease attacking us in a way that we found ourselves to be vulnerable. But the loss of vision is something that few of us have ever contemplated. We felt that there was a warranty issued on our eyes and we had the full use of our eyes for as long as we needed them. Then we find that we don't and an entirely different set of circumstances appears.

Now, it must be admitted that macular degeneration varies widely in the degree of severity with which it affects individuals. But for those with more severe type, such as this drug addresses, they have the problem of not recognizing

the faces of their friends, or their enemies if they have them. Also, they are not able to drive in a society where an automobile is as automatic a feature as a horse once was out West, or even almost an appendage of oneself--the automobile--is taken away.

In addition to that, the inability to read to varying degree, whatever it might be, is also a very serious detraction from quality of life. That blue sign over there; it is that entrance right there past the blue sign--of course, you can see it. And does this bus go to Amherst? Well, the drive is too busy to answer you so he nods and you don't see him nodding--these are not major events but they have a cumulative effect and what is very difficult for a great many of us to understand fully, because we don't choose to, is that macular degeneration is a progressive disease. As the years go by; the eyes do get worse whether we have the dry type or whether we have the wet type.

So, it seems to me high time that some action was taken to try to avert the further

incidence of macular degeneration in its various forms for the people who follow behind us. It has been said of older people that, as they think of their lives, the days grow longer and the years grow shorter. So, as the years grow shorter, all of us hope that somewhere--like Dr. Jonas Salk finding the cure of polio back in 1954--something may appear that will give us some surcease from the anxiety, and the apprehensions, and the limitations of macular degeneration. Thank you.

DR. DUNBAR: Thank you. Now I will ask speaker number four to come to the podium.

MR. AUGUSTO: Good afternoon. I am Carl Augusto, president and CEO of the American Foundation for the Blind, an organization that is dedicated to expanding the rights and opportunities of people who are bind or visually impaired in this country. Like Helen Keller before me who devoted 44 years of her life to the American Foundation for the Blind and its causes, I am always grateful to speak to governmental officials, corporate America and the general public on how we can improve the

lives of people who are blind or visually impaired.

In my 30-plus years working as a rehabilitation counselor and as an administrator in agencies serving the blind and visually impaired, I have seen first-hand the many difficulties faced by those who are losing their vision as a result of AMD, age-related macular degeneration. After living most of one's life, relying heavily on the sense of sight, not seeing well enough or seeing at all can certainly turn the world upside down for those people and their families. Add to that other physical ailments, physical disabilities, personal and social hardships that older people, many of them, experience the emotional and the functional adjustment to vision loss is very, very difficult.

Ordinary daily activities become challenging, if not impossible. If you can imagine not having the opportunity or not having the ability to read the morning newspaper, to drive to supermarket to get your groceries, to do your personal business, to read your personal mail, to cook for yourself--this is what is happening with

so many people losing their vision in this country. Moreover, it is difficult to adjust emotionally and functionally to a certain level of visual loss if that vision worsens next month.

One of the first clients that I had as a rehabilitation counselor was a gentleman suffering from age-related macular degeneration. He was about 50 years old and his deterioration rate was steady over the course of time, and he was really overwhelmed by this. His name was Jack. Jack had lost confidence in his capabilities. He felt that he couldn't do his job any longer. And, one of the things he said to me was, "just when I think I'm beginning to adjust, I lose more vision and the despair sets in again."

Well, his visual loss forced him to retire from his job long before he should have. It was a financial hardship to his family. He was staring at the walls every day and not feeling productive at home. It took an emotional toll on the family. His wife couldn't handle it any longer and she left and now he was on my doorstep, wanting answers to

how to live independently.

I remember thinking that, gee, if I had seen him a little earlier, or if the progression of his sight loss was not as significant I might have been able to help him realize that he could do his job still using alternate techniques or technology. But he lost his vision much too quickly and he did give up.

Now, my blindness is caused by a recessive gene disorder and it started when I was very young. When I was eight years old I started losing my vision and my loss was very gradual over the course of time. I became totally blind at about age 45. Some days I think I haven't reached 45 yet but that is just a couple of years ago. But that gave me an opportunity to learn the skills that I needed to function independently at home and on the job. I had an opportunity to tackle the emotional hurdles that inevitably arise with severe vision loss, and I truly believe I live a life that is as normal and satisfying as anyone's.

Now, AMD is the leading cause of severe

visual loss in our country, and this visually impaired population will continue to increase as the baby-boomers reach old age. Simply stated, we are outliving our eyes and delaying the effects of AMD or stopping the effects of AMD would give millions of people more time to adjust emotionally and functionally, to locate rehabilitation facilities, and to develop the skills that are so critical in helping them to function independently. If we can do this, any kind of slowing of the deterioration would be a blessing.

There are services for people who are blind or visually impaired. Low vision services that are delivered by specially trained eye care professionals enhance the remaining usefulness of your vision when you do have vision remaining. Other rehabilitation services are available from private and public agencies throughout the country to help you with personal management skills and also vocational skills. And, assisted technology is revolutionizing the way blind and visually impaired people function.

However, there are two problems. Many people with age-related macular degeneration and other visual loss don't even have a clue that these programs are available and they may not be in their own communities. Secondly, we don't have the funding in this country, federal or otherwise, to support sufficient services to meet the growing need for services for the increasing population of blind and visually impaired people. So, anything we can do to reduce the numbers of this population would be helpful in that regard.

In closing, blind and visually impaired people can live and work with dignity and success alongside their sighted peers. People can adjust and learn new skills and also to live independently. But many of them need time to develop. Many of them are not adjusting when their vision continues to deteriorate, and without a chance to learn to cope with vision loss gradually, I am afraid that too many people will be like Jack and will give up on themselves before they realize that there is help out there that could help them.

Thank you.

DR. DUNBAR: Thank you. Now I want to request that speaker number five come to the podium.

DR. ROSENTHAL: I am Bruce Rosenthal, Chief of Low Vision Programs at Lighthouse International, New York City and Mount Sinai Hospital. My organization paid my expenses. However, in the past I have had an unrestricted educational grant from Novartis for a booklet on vision function.

Over 75 percent of the visually impaired patients I have examined for the past 30 years have a diagnosis of age-related macular degeneration. I have been witness to how the devastating effects that progression severe vision loss, especially from the neovascular form of the disease, impact on an individual's day-to-day activities. I have seen how severe vision loss affects an individual's quality of life, impacts on their independence, lowers their self-esteem, and results in depression. In fact, clinical studies have shown

that over 57 percent of people with retinal disease have depression.

As a clinician, I am very concerned with retaining visual function. Neovascular AMD has the effect of destroying vital components of visual function. We are all familiar with visual acuity, as well as the importance of preserving it. But other vital components of vision are also irreparably destroyed by the effects of AMD. They include contrast sensitivity, and in lay terms that is how much a pattern must vary in contrast to be seen, and has become increasingly recognized as an important factor in influencing the quality of life. We are also interested in retaining usable visual field, color perception and stereo-acuity, just to name a few.

The medical advances, as we all know, that have taken place in the past 30 years have been few and far between. However, thermal laser as well as PDT have really helped to slow the progression and maintain visual function, and one example that I will give to you as a clinician is that the early

patients I was seeing with low vision would go from 20/800 down to light perception. My patients now usually fall in the end stage between 20/200 and 20/400. Yet, serious vision loss continues despite these interventions, as we know.

As Carl Augusto mentioned, we seem to have an impact, however, with vision rehabilitation. As a low vision clinician, I have seen that individuals with AMD who have access to the latest treatments benefit more from vision rehabilitation services as well. These individuals have a greater success rate in the use of low vision optical prescriptive devices, absorptive lenses, as well as high tech and electronic aids. These people can continue to be employed, travel independently, manage their own affairs, maintain their own residence and perhaps even drive. Again, I recommend that you consider the treatment that will help preserve visual function and its benefits to society.

DR. DUNBAR: Thank you. This concludes the five members of the public that have registered

to speak at the open public hearing. However, there are some additional members of the public that have approached us requesting to speak and, time permitting, they will be allowed to come to the podium and give two-minute presentations. So, I will ask if there are any other members of the general public that wish to come forward at this time. Thank you. We have someone coming forward.

DR. LISS: I am Bob Liss. I am an ophthalmologist in practice, retinal diseases, in Baltimore. I congratulate the sponsors and certainly hope that this is approved.

I did want to comment that I am concerned about the problem of endophthalmitis in terms of the fact that the drug is very broadly applicable drug that covers all subtypes of choroidal neovascularization so it will be used much more widely, and the people using it in the community, whether they are retinal specialists or ophthalmologists who are not retinal specialists, because of the more broad range of the indications, are selected different than the investigators. The

investigators, as much as the sponsors, have wanted to have a real-world test of the trials. The investigators are trained extensively and controlled much better than the outside area. So, I do think that control of complications, particularly endophthalmitis, is important.

The second thing is a comment about the quality of life. There was just a discussion about contrast sensitivity and visual fields, along with the early discussion about ERG and I think these types of things should be included in future evaluations. Thank you.

DR. DUNBAR: Thank you. Are there any additional members of the public that wish to come forward?

[No response]

Committee Discussion

At this point then we will open up for general discussion among the committee members, taking into account the presentations we have heard from the public. Are there any comments at this time? Dr. Lehmer?

DR. LEHMER: I was going to mention earlier, and I was glad one of the public speakers, Mr. Rosenthal, mentioned about contrast sensitivity. A lot of my patients who have the same level of visual acuity function very differently on similar behavioral tasks in the office and when we test their contrast sensitivity it varies greatly. So, it seems like I would second the motion of including that as a measure.

DR. DUNBAR: Dr. Chambers?

DR. CHAMBERS: The agency certainly agrees they would like to be able to use contrast sensitivity as a measure and certainly believe it is a measure of visual function. The difficulty with using contrast sensitivity in an assay is figuring out which contrast sensitivity is the most appropriate, and if you find a difference in one frequency versus a different frequency what does it mean? If you have any guidance on which frequencies are more important than other frequencies, we would love to hear those comments.

DR. DUNBAR: I am interested in the

comments about off-label use of the drug. I think this is insightful because once the drug is available to doctors--for example, would a doctor perhaps instill it into the anterior chamber for a patient with rubeosis? And, this is a conceivable possibility. Do we know anything about endothelial cell toxicity? This is a question actually for the sponsor.

DR. ADAMIS: The question is an important one. We did not look specifically at endothelial cell counts. We didn't do any specular microscopy. All we can report is that over the 54-week period there did not appear to be an increased incidence of corneal edema.

DR. DUNBAR: Is there any preclinical data that might guide us about this question?

DR. ADAMIS: In the preclinical animal studies there was no finding of corneal edema as a function of the use, but in the animals as well, to my knowledge, specular microscopy was not done.

DR. GUYER: Just as far as a comment on other uses, the sponsor right now is presently

looking at other important diseases in trials. We finished our Phase II program of diabetic macular edema and actually, hopefully in the fall, we will be talking with the agency about putting together a Phase III program. As you mentioned, there are a lot of conditions in the eye but today, you know, we are specifically talking about the indication for age-related macular degeneration.

DR. DUNBAR: As a pediatric ophthalmologist, I am interested in retinopathy prematurity. Do you have any comments about its use in that situation?

DR. ADAMIS: Theoretically it is a drug that I think may prove useful in retinopathy prematurity but the data that I showed you is that, you know, VEGF is required for normal vessel formation and the conundrum has always been, well, how can you block the bad vessels and leave the good vessels alone? But it look like by targeting 165 we may be able to do that. So, that is something we would consider doing in the context, obviously at some point in the future, as a

clinical trial. We wouldn't recommend off-label use at this point.

DR. GUYER: Also, in addition to retinopathy prematurity to look at in the future, and we mentioned the diabetic program also, we are also presently in a Phase II program for retinal vein occlusions and the macular edema that comes from that. In fact, if we could just go to E-158 for a second, it just lists a couple of the trials, if anyone is interested.

[Slide]

In addition to the diabetic program, we presently are studying, as I said, retinal vein and also we have a small program with Emily Chiu, of the National Eye Institute, on von Hippel Lindau tumors because of the increased permeability of those lesions. We are considering, but have not started yet, trials for pathological myopia and histoplasmosis where, again, choroidal neovascularization is associated; sickle cell retinopathy; iris neovascularization, as was earlier mentioned; and proliferative diabetic

retinopathy. Those are presently under consideration.

DR. DUNBAR: Are there additional comments from the committee at this time, especially pertaining to the public hearing?

[No response]

Now I would like to shift our emphasis once again to the general discussion that we began this morning and see if there are any other comments in general from the committee before we move on to the questions. I will poll the committee members one by one.

Dr. Chinchilli, do you have any additional comments?

DR. CHINCHILLI: No, I do not.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: No, I do not.

DR. DUNBAR: Dr. Steidl?

DR. STEIDL: No, I don't.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: No, I do not.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: No, I don't.

DR. DUNBAR: Dr. Gates?

DR. GATES: None.

DR. DUNBAR: I have no additional comments. Dr. Miller?

DR. MILLER: No.

DR. DUNBAR: And Mr. Kresel?

MR. KRESEL: No, I do not.

Questions

DR. DUNBAR: At this point then let's move on to a discussion of the individual questions posed by the FDA. I will read the individual question and open up the question for general disease and at the end of the discussion poll each member.

The first question reads, has sufficient data been submitted to evaluate the efficacy and safety profile of pegaptanib sodium? Excuse me, I was operating from an older list.

Back to question number one, based on the inclusion/exclusion criteria, are there patients excluded from the studies that you believe need to

be studied? Is there any general discussion about the inclusion and exclusion criteria? I am going to go ahead an poll each member. Dr. Chinchilli?

DR. CHINCHILLI: No, I don't have any comments.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: No, I don't have any additional comments.

DR. DUNBAR: Dr. Steidl?

DR. CHAMBERS: Can I interrupt? Besides saying you don't have any comments, if you think it was appropriate--it is at least somebody saying you think they were appropriate as opposed to just no comments. Thank you.

DR. DUNBAR: Let's start back again with Dr. Chinchilli.

DR. CHINCHILLI: Well, I am not that familiar with ophthalmological clinical trials, but the criteria seem appropriate to me.

DR. DUNBAR: And Ms. Knudson?

MS. KNUDSON: I think the criteria are appropriate and in terms of sufficient data, my

only concern is what we have expressed before, long-term use.

DR. DUNBAR: Dr. Steidl?

DR. STEIDL: I don't believe that there were patients excluded that need to be studied.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: I agree with Dr. Chinchilli and the other members so far.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I agree that the criteria seem appropriate.

DR. DUNBAR: Dr. Gates?

DR. GATES: I am satisfied with the inclusion/exclusion criteria.

DR. DUNBAR: I concur with the rest of the committee. Dr. Miller?

DR. MILLER: I concur.

DR. DUNBAR: And Mr. Kresel?

MR. KRESEL: I agree with what the rest of the committee has said.

DR. DUNBAR: We will move to question number two, visual acuity measurements were

conducted using the ETDRS scale placed at 2 meters from the patient. The validity of the ETDRS scale was established based on readings at 4 meters. Are the visual acuity findings sufficiently robust to overcome the potential bias introduced by visual acuity measurements at 2 meters? Dr. Chinchilli?

DR. CHINCHILLI: We haven't discussed this although it was mentioned by the agency. You know, the fact that there is a control group, the sham group, and that you still see differences is encouraging. The question is whether or not there is some sort of interaction. I mean, would the sham group not have a bias when it is done from 2 meters whereas the dosed groups would? You know, I don't know if there is any logical explanation for something hypothetical like that happening. It doesn't seem like a major issue but I would like to hear the ophthalmologists talk about this issue.

DR. DUNBAR: Then I will open this up for general discussion before polling each individual committee member. Dr. Lehmer?

DR. LEHMER: I was just going to say I

wanted to hear what the statisticians had to say because when we are talking about robustness of data, you know, I wouldn't know where to draw the line on are these numbers robust enough to overcome that difference. But I hear what you are saying, that this is a comparison between groups that were tested under the same conditions so my assumption would be that the relative difference would still hold up whether it is 2 meters or 4 meters.

DR. DUNBAR: Dr. Chambers?

DR. CHAMBERS: I will just clarify a little bit. There are some differences in other areas such as adverse events which might lead someone to recognize which group they were in even if they were not able to tell from the actual procedures, such as some of the floaters, such as some of the other many adverse reactions which may lead them to, either appropriately or inappropriately, believe they were in a group. The concern is that there may be potential unmasking because of some of the adverse events that then may lead to differences, and the issue that there is

more variability with measurements at 2 meters versus 4 meters, although we don't have good quantitation on what that is.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: So, Dr. Chambers, is this a possible way of getting around this problem? I feel the data is good enough right now at 2 meters. Because there is a concern, could future studies be requested to be at 4 meters from the start for the small chance that there may be a problem?

DR. CHAMBERS: It is the agency's recommendation that they be at 4 meters to avoid the issue even coming up. Were we talking about a single letter we probably wouldn't be asking this question either. We would say, well, that is definitely within what the variation is. You may choose to believe, well, it takes 16 meters before you even get one line; this is a three-line change so we think there is enough robustness in the findings and robustness in differences in visual acuities that, while we would have not like to have had it, it is still okay. Or, you may say there

just is no way to go and tell and the agency needs to deal with it as best they can.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Though it would have been nice if it had been done at 4 meters, there appears to be enough robustness of the data that I accept it at 2 meters. Is that a good paraphrase of the way you had said it?

DR. CHAMBERS: I did not want to put words in anyone's mouth. I was trying to put out examples of the type of information we are looking for in comments.

DR. PULIDO: That would have been the way I would have said it without you having said it.

[Laughter]

DR. DUNBAR: I have a question for the agency. Was this an agreed upon aspect of the protocol prior to commencing the clinical trials, or was this a point that came up in the analysis later on?

DR. CHAMBERS: The agency, having had the ETDRS done under an IND, is fully aware of how the

protocols were written for ETDRS and has always assumed that if someone wrote ETDRS that they meant that they would do visual acuities at 4 meters. We have come to find out since that time that that is not the interpretation necessarily in the whole community and so there were clinical trials that were started using the charts but moving them to different distances and people continued to call it ETDRS even though it does not meet the technical protocol of ETDRS. In this particular case we were aware of the difference after the trials had started. To the extent we were aware of them before the trial start, to the extent that we were aware of them during the trials, we have made those comments but in some cases we are aware that there were trials that started before we were able to comment on it. Then you would be caught with the equal question of do you change the protocol in midstream or do you run the protocol the way it was started, even if you would have preferred to do it a different way?

I will let the sponsor comment on their

own but it is my understanding the choice--and we do fully understand it--is to continue the protocol, at the point that you recognize there is a difference, the way it was written so that you don't raise further questions about, okay, you have changed the protocol. What would have happened had you not changed the protocol? So, we are left with the data that we have. We obviously don't encourage it in the future but this is what we have.

DR. DUNBAR: I have a question for the sponsor. Was every center done at 2 meters? Were they all uniform throughout the protocols?

DR. GUYER: Could I have slide 14 up, please?

[Slide]

First, yes, they were all standardized. I think Dr. Chambers summarized very nicely in the morning the difficulties with 2 meters versus 4 meters. When we started the trial our thought process was, first, that historically other trials were done at 2 meters, most of the other trials

were for this condition. Part of the reason was that in order to be able to read all of the letters on the chart, some patients would not be able to do that at 4 meters. So, our thought was we could get more patients to see at the baseline visions and at week 54 on the chart and not have to move up to 1 meter.

But certainly the FDA has presented very, very good information why 4 meters should be considered as well. There is no perfect testing distance. I think Dr. Chambers also, on his slide, said it very well, that the key factor is if masking is good and if you have some kind of rigid way of making sure that the patient didn't lean or move, then 2 meters is certainly a good testing parameter. The real potential biases at 2 meters have to do with two things. One is accommodation which, obviously, in this population because of presbyopia is not an issue. The second is the leaning that Dr. Chambers mentioned.

Now, we have randomization which certainly helps. So, we would hope that good randomization

and masking should be equal between sides. But we also have some very important quality control information.

[Slide]

We had very vigorous training and monitoring of the visual acuity examiners before the trial and during the trial. In fact, we had over 450 audits performed in all of the centers throughout the world. And, one of the questions that was looked at was, was proper patient positioning, such as leaning, prevented by the acuity examiners? You can see that in these 469 audits, 98.3 percent of the examiners did use proper patient positioning, which comforts us that at least based upon this quality control we don't believe that the patients were leaning forward.

We also have good evidence of proper masking. All groups, the active groups as well as the shams, all got 8.5 of the 9 injections. So, that suggests that masking was good. Similarly for discontinuation rates and reasons, which you can see in the FDA briefing book.

[Slide]

Actually, when we did a trial for macular degeneration a number of years ago we devised this measuring stick which also must be used at every examination. Here you can see a visual acuity examiner to actually remind the visual acuity examiner always to be sure that the patient is at the right distance and that the patient doesn't lean forward. This, I think combined with the quality control, helps us.

Also, in Dr. Chambers' questions about masking and floaters, which is a very good question, we actually have looked to try to give us some comfort that there was no difference in the responder rate of patients who had floaters and didn't have floaters.

[Slide]

This shows that whether the patients had floaters or didn't have floaters we see an active treatment effect for both. So, we tried to look at the data from as many possibilities of potential unmasking and did not see anything. So, we have

some comfort I think by the quality control and by the good masking in the trial that 2 meters was probably not an issue. But we certainly share with the agency that in future trials 4 meters are preferred. We wish more study centers, as Dr. Chambers mentioned, had 4-meter testing which has also been part of our thought process, that it is difficult to get 117 centers with rooms that big. But we are working in other trials to do 4-meter testing after these discussions.

DR. DUNBAR: Thank you. Are there any other general comments for discussion before individual polling of the committee members? If not, I will ask each committee member to answer the question are the visual acuity findings sufficiently robust to overcome the potential bias introduced by visual acuity measurements at 2 meters? Dr. Chinchilli?

DR. CHINCHILLI: Yes, I believe the data are reliable even though the measurements were taken at 2 meters. I was comforted by some of these quality control issues that the sponsor

addressed and was prepared to address.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: I will echo what Dr. Chinchilli said.

DR. DUNBAR: Dr. Steidl?

DR. STEIDL: Yes, given the significance, the audits presented and randomization, I am comfortable with them.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: I am comfortable with the robustness of the data.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I am comfortable with the robustness of the data.

DR. DUNBAR: Dr. Gates?

DR. GATES: I am also satisfied. In examining patients on a day-in and day-out basis I always ask them to lean forward for these different tasks, and with this randomization not picking on any particular segment of the patient population, I know some will and some won't even if they are physically able or not able. So, with this

randomization I am very satisfied with the robustness.

DR. DUNBAR: I concur with the other comments to this point. Dr. Miller?

DR. MILLER: Based on what Dr. Chambers and also the sponsor has had to say, I concur.

DR. DUNBAR: And Mr. Kresel?

MR. KRESEL: I agree with the rest of the committee.

DR. DUNBAR: We move to question number three, has sufficient data been submitted to evaluate the efficacy and safety profile of pegaptanib sodium for the treatment of the neovascular form of AMD? If not, what additional data are needed? I would like to open this for general comments and discussion.

[No response]

Then I will begin by polling Dr. Chinchilli.

DR. CHINCHILLI: You have to start over there next time--I am kidding! Well, based on the discussions we had this morning, it sounded to me

as if some of the committee members want to see more data on long-term safety and use and continuation, you know, how long is it necessary to continue. I mean, I have no idea how long of a period of time we need to have data to assess long-term efficacy and safety. So, I am not going to make a judgment on that but it seemed like it was a concern to many of the committee members.

DR. DUNBAR: I will ask you to address each part of the question, the first being has sufficient data been submitted to evaluate efficacy and safety profile?

DR. CHINCHILLI: Yes, I sort of glossed over that. Yes, I believe it has.

DR. DUNBAR: You mentioned the additional data part as well. Any further comments on that?

DR. CHINCHILLI: No, I don't have anything else.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: I think from what I have read and heard that sufficient data is available, and additional data I would like to see is how long

would a patient need to use this; how much safety is there after several years of use. Those are my concerns.

DR. DUNBAR: Dr. Steidl?

DR. STEIDL: Well, there is a lot of additional data I would like to see but I don't think that additional data is required ultimately.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Yes, I believe that sufficient data has been submitted to evaluate the efficacy and safety profile, and it appears to me very efficacious and safe. I do believe that postmarketing surveillance for ERG, visual field and subsequent vision would be worthwhile in a subgroup of patients.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I feel that there is sufficient data to show the efficacy and safety within the parameters of the study, and would echo the comments of Dr. Pulido.

DR. DUNBAR: Dr. Gates?

DR. GATES: I also believe sufficient data

has been submitted for efficacy and safety.

DR. DUNBAR: I concur with the comments of the rest of the committee about sufficient data for efficacy and safety, and I concur with Ms. Knudson that some type of postmarketing surveillance for long-term efficacy be continued. Dr. Miller?

DR. MILLER: I concur with regard to the data for efficacy and safety, however, I am really concerned, as you have also mentioned, with regard to how long a patient should be taking this particular medication.

DR. DUNBAR: Mr. Kresel?

MR. KRESEL: I think sufficient data has been submitted to evaluate efficacy and safety for one year, and I will leave it to my ophthalmology colleagues to determine if longer-term data is needed.

DR. DUNBAR: Question number four reads, are additional analyses of the current data needed to understand the efficacy or safety of pegaptanib sodium for the treatment of the neovascular form of AMD? Dr. Chinchilli?

DR. CHINCHILLI: I mentioned this, this morning, about the time to treatment failure. I don't think it is going to have an impact on this particular situation here but, you know, it would be interesting to see Kaplan-Meier survival curves. I think there was one point where the sponsor had flashed a slide up there and then took it off because they were addressing some other issue with that question. But I think the agency in particular should consider this for future studies for future sponsors. I mean, the disease is one that is progressive so you are going to reach the point where it has progressed to the point of concern which, everybody has been telling me, is greater or equal to 15-letter loss from baseline.

So, I think it should be analyzed in that manner. As I said, I don't think it is going to affect this particular situation with this particular drug. So, I don't see the need for additional analyses now but I think the analyses I am proposing would be more accurate and not rely so much on data imputation.

DR. DUNBAR: I wonder if this can be the answer to our question about how long the drug should be taken. It seems like this type of analysis might answer that question. DR. CHINCHILLI: That is possible, yes.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Point of clarification, there is a question on board by Dr. Chinchilli. I don't think it is going to make a difference. I don't think it is going to change what we have found but since the question is out there to either the FDA or to the sponsor, do they have the answer to it?

DR. DUNBAR: Will you repeat the question?

DR. CHINCHILLI: Do you have the Kaplan-Meier survival curves?

DR. CHAMBERS: We have not chosen to ask for it because we have information, not on this drug but on other drugs, that time-to-event is not indicative of what you see at year one and at year two. So, we have not pushed for this type of analysis. In fact, we believe that what you see at month three and month six is frequently in the

wrong direction for what you see at one year and, consequently, have not asked for the time-to-event analysis because we see them reverse.

DR. CHINCHILLI: But you can use the Kaplan-Meier survival curve to get a more accurate indication of what is happening at one year. I agree if you think three months and six months is too early, but you can use the curve, the survival curve to get a better estimate of what is happening at one year because it accounts for all the censoring, the dropouts and the terminations that occur.

DR. CHAMBERS: You are right, if we don't take people out as a single event and allow them to either come in or come back out as they go through that endpoint, I absolutely agree. I am just going through the reason why we have not in the past used that because we did not want an answer that happened to be less--we didn't know exactly where the point is that is potentially confusing. We know three and six is not. We have not known about nine months. In some cases with some drugs it

hasn't made a difference. With this particular drug you don't see reversals. So, what you learn early on does appear to be continuing later on. That is just not true of every particular product so we have not known ahead of time when to use it and when not to. But I absolutely understand what you are talking about. We just have not looked at those particular analyses and I don't know if the sponsor has or has not.

DR. GUYER: We have. Would you like us to show it?

DR. CHAMBERS: By all means.

[Slide]

DR. GUYER: This is the Kaplan-Meier estimate of the first observed loss of 15 letters of vision with ITT and, again, it is consistent with the other endpoints we showed you earlier today, that the active treatment groups at all of these data points with time show a treatment effect compared to the sham.

DR. DUNBAR: Dr. Pulido, do you have any other questions regarding this?

DR. PULIDO: No.

DR. DUNBAR: Dr. Chinchilli?

DR. CHINCHILLI: No, that is what I wanted to see. DR. DUNBAR: Okay. In our polling we kind of moved back to a general discussion. Dr. Chinchilli, you indicated that that satisfied your question?

DR. CHINCHILLI: Yes, it did. That was the additional analysis I would like to see but, again, I didn't expect to see anything different than that but it is still nice to see it, and that the sponsor had considered it.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: I will pass on the question of analysis of the data.

DR. DUNBAR: Dr. Steidl, are there additional analyses you would like to see?

DR. STEIDL: No, my impression is that additional analyses won't change the efficacy and safety profile.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: No additional analyses are

needed.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I agree, no additional analyses are needed.

DR. DUNBAR: Dr. Gates?

DR. GATES: No additional analyses are needed.

DR. DUNBAR: I concur. Dr. Miller?

DR. MILLER: I concur.

DR. DUNBAR: And Mr. Kresel?

MR. KRESEL: I concur.

DR. DUNBAR: Moving to question number five, has the concomitant use of PDT therapy with pegaptanib been explored sufficiently? Are there concerns with using this product concomitantly with PDT therapy? I would like to open this for general discussion. No additional general comments at this time? If not, as I poll you individually just please try to address the two parts of this question. Dr. Chinchilli?

DR. CHINCHILLI: Well, I think it was a good idea to not make exclusions in the study for

PDT therapy. Given that situation, I thought the sponsor did a reasonable job of analysis to account for that. So, I think, you know, that is a hard one to answer for a statistician. It hasn't been explored sufficiently. You know, we are never satisfied. So--

DR. PULIDO: You have proven that already!

[Laughter]

DR. CHINCHILLI: I don't think I will get invited back. You are going to kick me back to my other committee, I know that.

You know, the designs were reasonable. In the inclusion criteria it was good to see that they included that since PDT therapy seems to be something that is important for this disease. So, I think I have answered the first question.

Are there concerns with using this product concomitantly with PDT therapy? You know, given the circumstances and the way the trials were designed, I thought the sponsor showed that, given all those limitations, the sham group was the one that ended up having to have more PDT therapy,

showing efficacy for the product. It didn't seem like there were safety concerns. I didn't see any issue. Although the numbers were small, there didn't seem to be any safety issues when it was used concomitantly. But, you know, the trials weren't designed specifically to look at that.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: I am comfortable actually answering yes to the first and I have no problem with the second personally.

DR. DUNBAR: Dr. Steidl?

DR. STEIDL: I think it has been explored sufficiently and I don't have concerns about concomitant use. I think we would all like to know ultimately if there is a synergistic effect. That is what is ultimately going to be an issue.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: I agree with my esteemed colleague to my left.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I don't feel that the numbers involved were large enough but, again, the study

was not designed to specifically look at answering this question. So, with regard to the lack of difference between the groups, I guess within the small numbers that were shown I would have to say that there doesn't appear to be enough concern for further study of this. So, I guess I would have to just caution about the fact that there are small numbers but the data that they do have don't raise a sufficient concern for me.

DR. DUNBAR: Dr. Gates?

DR. GATES: Yes to the first question; no, to the second.

DR. DUNBAR: I concur with the rest of the committee. I think that it was comforting that both the agency and the sponsor numbers, even though they were small numbers, they agreed in the ways that they looked at this and so I concur. Dr. Miller?

DR. MILLER: I concur but I was concerned about the small numbers but I will concur with everyone else.

DR. DUNBAR: Mr. Kresel?

MR. KRESEL: I think the design of the study tends to answer the question, and when you have an all-comer study, you know, you mimic real-world use and I think that answers at least the question of the safety of using the two products together. It wasn't designed or intended to talk about any additional efficacy parameters so if people have questions about that they may want to look into that at a later date, but it certainly answers the question on the safety of using the two products together.

DR. DUNBAR: Question number six reads, do the route and/or frequency of administration of the drug raise any concerns that are not addressed by the studies? Is there any general discussion about this question?

[No response]

Then we will move on to individual polling, starting with Dr. Chinchilli.

DR. CHINCHILLI: I don't feel qualified to answer this. I would like to hear the ophthalmologists respond to this. Do I have to

give an answer?

DR. DUNBAR: No.

DR. CHINCHILLI: Thank you.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: Of course, I feel similarly to Dr. Chinchilli but I would like to say that if, indeed, this is the route and if, indeed, it is the amount of time between injections that patients will actually be going through, I wondered to myself whether people would be willing to come back that frequently for an invasive procedure. Then I thought, well, these are highly motivated patients and they probably would be. So, I am all right with this.

DR. DUNBAR: Dr. Steidl?

DR. STEIDL: Well, I guess maybe more so than others here I believe the route and the frequency are a big issue and do raise significant concerns but, in the spirit of the question, I do think they were raised by the studies and they were discussed by the company. So.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Just one question to the FDA, were less often injections evaluated, i.e., every three months? And, can I ask the company if they have any data on less often injections?

DR. ADAMIS: Let me tell you briefly about what we are doing because we would like to limit the number of injections as much as possible. There is the ongoing 1006 study which is a pharmacokinetic study where we are looking at various doses, trying to determine what the relevant half-life in the vitreous is in people. Recall, when we designed the study we used the monkey half-life of four days.

The other thing we are doing is we are determining in the laboratory the relevant inhibitory concentration when you administer this via intravitreous injection.

Once we have those two pieces of data in hand, if there is evidence that we can dose less frequently or there is a more optimal way that is certainly something that the sponsor is willing to consider. But right here, today, what we have is

that the 0.3 at every six weeks appears to be safe and effective.

DR. PULIDO: In that case, as far as the route and frequency of administration, I think until new data shows it can be done less frequently the data is acceptable to me. Again, I do have the long-term concerns that I have mentioned before because of the neurotrophic effect of VEGF.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I think the concerns have been addressed adequately. I know with regard to injecting acyclovir agents for CMV retinitis it seemed we were jumping to implants fairly quickly and this population that was studied were highly motivated, possibly more highly motivated than patients who are not participating in a clinical trial. So, there may be less enthusiasm or less compliance with coming in for every six-week injections but I think within the realm of the study I don't have any concerns.

DR. DUNBAR: Dr. Gates?

DR. GATES: No additional concerns.

DR. DUNBAR: I think it is interesting that in the study the sponsor has shown that they were able to retain well greater than 90 percent of their participants even when they were receiving between 8-9 injections. So, yes, of course, there are concerns for anyone receiving multiple intraocular injections, however, to the best possible in a clinical trial situation, I think they have been addressed. Dr. Miller?

DR. MILLER: Yes, I would agree that they have been addressed but, at the risk of being an N of 1 study myself, I am a motivated person and I am concerned that someone would have to go through the discomfort so many times. So, I just wonder if there isn't a way of delivering it some other way, other than through an injection, but I am not an ophthalmologist. Thank you.

DR. DUNBAR: Mr. Kresel?

MR. KRESEL: I agree with Dr. Dunbar. I think certainly there is data for nine injections in the first year and there will be data very soon for 18 injections cumulatively. How many

injections a patient can endure over time cumulatively I don't know, but patients tend to vote with their feet and so in the end you find that out anyway. So, I think that for now the data is adequate.

DR. DUNBAR: Question number seven reads, endophthalmitis was observed in approximately two percent of patients in these studies. What is the optimal follow-up needed to minimize the impact of potential endophthalmitis cases? Is there any general discussion about this before the individual polling?

DR. CHINCHILLI: Well, I am not quite sure I understand the question. I mean, are we talking about optimal follow-up in the individuals who have been diagnosed with endophthalmitis or are we talking about the general population? I mean, it is not clear what the agency is asking.

DR. CHAMBERS: Let me clarify. We are potentially talking about if we were to approve this product and attempt to label it. Because this is an event that could occur, we are looking at how

frequently we should be recommending people come back. Endophthalmitis is more easily treated early rather than late. Are there recommendations on how often people should come back to be observed? Obviously, in the first week is when the cases were observed. Are there signs that we should be putting in the labeling that should be warning patients on things to look out for that should suggest that they see somebody earlier rather than later? Basically, we are looking as much as possible for additional labeling comments.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: It seemed to me that all the cases of endophthalmitis presented within one week. Was that correct? It is always an issue if something is relatively infrequent, such as this, should everybody be screened, say, two days or three days afterwards? It seems like when the potential risk is high, as it is in endophthalmitis, that it is worth doing that.

DR. DUNBAR: I think it was interesting that the sponsor designed their study so they had

telephone follow-up at three days, and they did pick up a significant number of those cases through that telephone follow-up. I was trying to compare this in my mind to, say, a cataract surgery where maybe a patient will be seen at day one and day seven and that is another procedure with the risk for endophthalmitis. However, the extra precaution of the three-day follow-up seemed to provide benefit because their patients also did better in general than patients with endophthalmitis. I wonder what the rest of the committee members think about this.

DR. PULIDO: I think that many were found at four days. So, was it that they called at three days and that they noticed that they were having a problem and so they came back on day four?

DR. DUNBAR: Maybe the sponsor can comment on this.

DR. ADAMIS: If we could call up slide 128, just to remind the audience?

[Slide]

Three of them were picked up on their

phone call at days three and four. There were two questions we asked them: "How are you feeling? And, "how is your vision?" That is how they were captured.

Eleven, the majority, walked in on their own, went back to the doctor's office, between days two and five. Then, the remaining two were during the one-week follow-up exam. That is how everybody was diagnosed. It was actually the one-week period.

DR. DUNBAR: Dr. Gates?

DR. GATES: Do you have an idea how many people you called and screened that were negative on that day-three phone call?

DR. ADAMIS: Everybody was supposed to get called so presumably everybody else was negative.

DR. DUNBAR: Are there any comments from the committee about the specific recommendation? Mr. Kresel?

MR. KRESEL: Going back to my earlier pragmatic approach because I do write labeling, it seems to me that probably somebody should have a

recommendation and probably some patient educational material so that patients will understand what to look for and call their physician. If 11 of them showed up in the office on their own, they were probably told by their investigator that if you have these particular problems you should call me.

So, we probably should recommend some kind of patient education. It seems like a rather simple, more pragmatic approach. You are certainly not going to expect a busy office to be calling every patient all the time. So, having patients understand what to look for and knowing when to call probably makes more sense.

DR. DUNBAR: Are there any specific recommendations of signs or symptoms that the committee wishes to have included in the labeling? For example, say, a patient had their family member read the labeling to them like patients sometimes are wont to do if they are not feeling well? Any specific recommendations for the agency? Dr. Steidl?

DR. STEIDL: I don't have any because some endophthalmitis can present with a quiet looking eyes, some without pain. I have a lot of patients walk in, not realizing that they have lost significant vision. And, maybe this is a particular type of population and maybe with the right education you can prevent that to some degree, but I think if we rely on the patient it is dangerous. As far as specific recommendations, I don't know, you have a sudden enough endophthalmitis on day one or day four--it can happen any time. So. Phone calls I guess in lieu of everyday exams might be reasonable. I am not really sure.

DR. DUNBAR: Should the labeling mirror the study design with visits at one day, a phone call at three days and visit at one week? Or, should the labeling provide--you were mentioning there was a patient education component, there is a physician examination component, and it seems like to protect patients the labeling should reflect both of these, as was designed in the study. Dr.

Lehmer?

DR. LEHMER: The comments have been made that the outcomes of these endophthalmitis cases were very good compared to, say, postoperative endophthalmitis after cataract surgery and maybe that is because of the rigorous follow-up and maybe that should be the new standard. I know there is no FDA label saying everybody should get examined one day after cataract surgery, but I suppose it would be easier to make it a standard if the recommendation to change the protocol was to make it a more surgical approach, meaning a sterile field. Then perhaps a recommendation for a follow-up should also be more along those lines--this is a surgical procedure and a day-one check or phone call and a week-one check would be appropriate.

DR. PULIDO: I disagree. The volume of patients would be extraordinary on day one. If we are going to increase the follow-up, I think following protocol and having a phone call at day three would be probably more acceptable to the

patients. For some of these patients it is hard to come back. It is not as surgically invasive as other procedures. I don't recall right off the top of my head how many came back at day one with endophthalmitis in this group but I think it was only one. To pick up one case, you would have tremendous hardship for these patients. I think if you want to go that route, a phone call at day three and then follow-up at week one would be much better both for the patient and for the volume of cases.

DR. DUNBAR: I would like to recommend that the sponsor and the agency work together to include education in the label, such as to return if symptoms of redness, pain and vision loss--very brief endophthalmitis education and to incorporate some agreed upon follow-up schedule. Are there any other general comments?

DR. MILLER: I would disagree with that. I think that. I think we need to remember that some people don't always have someone there to read for them. So, if there is a way of getting the

information to them and making sure that they know what to look for before it happens, that would be helpful.

DR. DUNBAR: If there is no more general discussion let's resume the individual polling. Dr. Chinchilli, have I already begun with you?

DR. CHINCHILLI: Sure, you did! It sounds like some sort of form of education is necessary or follow-up by the ophthalmologist's office. So, I really don't know what to recommend but obviously this is of major concern so some form of follow-up or education is necessary and I just can't make a recommendation.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: I think it is quite clearly physician and patient education material that needs to be developed. And, if patients can't read or don't have someone to read to them, they could have an audio tape which would describe what they need. That is not very expensive to do and it would be very simple.

DR. DUNBAR: Dr. Steidl?

DR. STEIDL: I agree with Dr. Pulido that probably more than one exam in a week is going to become prohibitive. I think a phone call is reasonable. The materials that we have for Visudyne are useful, and I think that, you know, when Visudyne was just coming out there were a lot of these meetings that explained to doctors how to manage their patients and I think this has to be impressed on them, how this needs to be done for patient education.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: I agree with Dr. Steidl.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I would still advocate the one day. I don't know many of our cataract surgery colleagues who have given up examining their postop patients one day afterwards. I think part of the message we might be sending by having a phone call be the only thing between treatment day and one week postop is that perhaps this is a fairly benign procedure, and knowing that a lot of surgical procedures are being considered by optometrists

these days we have to realize what kind of message we may be sending with our labeling. But I would agree that at a least a phone call on day three and an exam one week later is necessary.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Again, maybe I am missing something, Dr. Lehmer, but there was one case that I see here of endophthalmitis, in the chart on page 47, on day one. So, we are going to not pick up the vast majority of cases by seeing the patient on day one. What is it that we are going to pick up on day one?

DR. LEHMER: Well, that is true of this population, which is not thousands of patients. We would, therefore, pick up several patients over the population of the United States that would be patients receiving this treatment.

DR. DUNBAR: Dr. Gates?

DR. GATES: I recommend the phone call at day three with the specifics on redness, sensitivity, vision deterioration and pain to be in that phone call, so to speak, as a protocol. I

also concur with the one week postop visit. I think that is a good compromise between the two positions and I think that is appropriate with the standard of care of other intraocular surgeries.

DR. DUNBAR: I would like to recommend that very specifically patient education be addressed with the same sentence that Dr. Gates said, redness, pain, loss of vision, and that physician education with follow-up at least at the three-day and seven-day time periods be suggested. Dr. Miller?

DR. MILLER: I would like to strongly recommend that we have the patient education component as you have discussed.

DR. DUNBAR: Mr. Kresel?

MR. KRESEL: I think a combination of patient and physician education and follow-up visits is necessary. I will leave the timing to the ophthalmologist. But I would point out that finding one case in a thousand is not an insignificant number.

DR. DUNBAR: Question number eight reads,

are there adverse experiences that are of particular concern for this product? We will start with general discussion. In the absence of any comments, we will move to individual polling with Dr. Chinchilli.

DR. CHINCHILLI: Well, I didn't see any in the safety tables provided, other than the endophthalmitis--anything that looked drastically different from the sham group. So, I don't see anything to comment on for that one.

DR. DUNBAR: Ms. Knudson?

MS. KNUDSON: I agree with Dr. Chinchilli.

DR. DUNBAR: Dr. Steidl?

DR. STEIDL: I guess I have stated my case about endophthalmitis and, in fact, Dr. Liss' points, who came up and spoke, were well taken that although I think Visudyne has been well managed I think there are a lot of ophthalmologists who might consider doing this, people who don't normally do this type of thing in the community, particularly if there is a lot of hype about it. People are coming to their office, saying do you do this?

And, they have to say they don't. I am just concerned about the risk in the hands of people who are not commonly doing this. But in general I think the adverse experiences have been well discussed and addressed by the company.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: I guess the only other one that would be of concern is the retinal detachment and, again, patient education regarding signs and symptoms of retinal detachment would be worthwhile.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: I don't have any additional concerns. DR. DUNBAR: Dr. Gates?

DR. GATES: No concerns.

DR. DUNBAR: In echoing the previous comments, I was interested to read that the retinal detachment patients seemed like they were high risk patients for retinal detachments, patients with lattice degeneration or multiple small holes. I am wondering if there should be a precautionary statement in the label addressing this. It seems like common knowledge among ophthalmologists,

however, those patients certainly are at an increased risk for any retinal detachment and disturbing the vitreous in those cases could tip them over the edge. Dr. Miller?

DR. MILLER: Yes, I have a concern that was I guess an echo of what was mentioned earlier about potential individuals who don't do the procedure every day or who might not be as knowledgeable. How would we address that for the patients' benefit? Is there something that the agency or the sponsor can do to address that issue? I am asking Dr. Steidl.

DR. DUNBAR: Dr. Steidl?

DR. STEIDL: Well, I am probably not the right one to answer that, but these things do tend over time to work themselves out to some degree. I just think that by anticipating the problem in the way it is presented, marketed and the information is disseminated to the doctors who are going to do this initially we can, to some extent, circumvent some of these problems but I think you can't completely. So, I don't really have an answer.

DR. DUNBAR: If only the federal government could instill personal ethics in every doctor in the United States! Mr. Kresel?

DR. KRESEL: A comment on that, I am sure the sponsor will be doing all kinds of educational programs because it is to their advantage to have the drug used properly and have patients be successful on it. So, I am sure there will be all kinds of training programs out there. I don't have any additional concerns.

DR. DUNBAR: Question nine reads, vascular endothelial growth factor, VEGF, has been shown to be an important component in the development of collateral vessels in ischemic heart disease. Inhibition of VEGF in the systemic circulation could present a theoretical increased risk of symptomatic cardiovascular disease in the target population of elderly patients with AMD.

(a), Has the adverse event profile of the two randomized Phase III trials raised any concern over the possible systemic effects of this therapy?

(b), Is there additional monitoring that

should be in place for patients on pegaptanib sodium therapy? Is there any general discussion on this two-part question?

[No response]

Returning to the individual polling with Dr. Chinchilli?

DR. CHINCHILLI: Well, with respect to part (a), I think it is prudent to be concerned about possible systemic effects. Obviously, with the one-year data we were shown there wasn't any evidence of that, but there certainly can be cumulative effects over time so, again, I think what we described in one of the earlier questions in terms of having long-term follow-up and long-term data, you know, that certainly should be monitored in terms of there being some systemic effects.

DR. DUNBAR: How long do you think it should be monitored?

DR. CHINCHILLI: I have no idea. I don't know. In my experience with other diseases, administered locally and not systemically, it was

important to do that as well with those other situations, to monitor systemically because there could be buildup; there could be transference into systemic compartments. So, I would say it needs to be done but I am not an expert. I can't really comment on how long that should be followed.

Then, in terms of part (b), I have sort of touched on that but I really don't know what else to say, what additional monitoring there should be.

DR. DUNBAR: The sponsor mentioned that the earliest indication of some systemic effect may be blood pressure. Should there be labeling that says the patient should be monitored for blood pressure effects of the medicine?

DR. CHINCHILLI: That sounds reasonable.

DR. PULIDO: On the other hand, this is a population that is hugely at risk for having elevated blood pressure, and to stop a medication that may be helping their vision with the off-chance that the blood pressure elevation was from the medication and not their normal disease and normal lifetime I don't think is appropriate.

So, I think the amount in the systemic circulation is so small that something like that would just not be very reasonable.

DR. DUNBAR: Are there any additional generalized comments before we resume the individual polling?

[No response]

Ms. Knudson?

MS. KNUDSON: I would just go back to my concern for long-term monitoring. I would find out more about the effects of the drug and the effects on the people who are taking it.

DR. DUNBAR: Dr. Steidl?

DR. STEIDL: My answer to (a) is it does not raise concerns. I think the systemic profile looks reasonably safe and has been well studied. And, I don't think that additional monitoring, from my point of view, is needed with regard to the whole issue of approval but there are a lot of things I would love to see--again, is there an additive effect of PDT; quality of life issues; ERG data. If that can be added in any form at some

point, it would be useful.

DR. DUNBAR: Dr. Pulido?

DR. PULIDO: Has the adverse event profile raised any concerns? No. Is there additional monitoring that should be in place for patients? Just what I have mentioned prior.

DR. DUNBAR: Dr. Lehmer?

DR. LEHMER: My answer to part (a) is no, and I agree with Dr. Pulido on part (b).

DR. DUNBAR: Dr. Gates?

DR. GATES: No systemic concerns, and no on the second part also.

DR. DUNBAR: I concur that there are no systemic concerns, and additional monitoring for any specific things like blood pressure or liver enzymes or kidney function tests should be monitored. The items mentioned by the previous committee members I think would be useful. Dr. Miller?

DR. MILLER: No to part (a). The second part, just the long-term follow-up with regard to the patients.

DR. DUNBAR: Mr. Kresel?

MR. KRESEL: No to part (a) and just long-term follow-up on (b).

DR. DUNBAR: This concludes the individual questions for the advisory committee. At this point in time, are there any other generalized comments from any member of the advisory committee?

[No response]

Are there any additional comments that the agency wishes to make?

DR. SELEN: Arzu Selen. One comment I would like to make is about the systemic bioavailability. I believe that there has been some discussion on this and, yes, indeed, there isn't a lot of drug circulating the systemic circulation. Nevertheless, given such a huge molecule, there is some bioavailability from intravitreal administration. Even though levels are low, it is still detectable. I guess I have to compliment the company on the quality and quantity of the pharmacokinetic data they have submitted. Based on this, it looks like the drug in humans has

a half-life somewhere around 10 days, and also ranges from 2-19 days in individuals. So, you know, there is considerable amount of drug remaining after a single dose. Nevertheless, the levels that you are looking at are at 0.3 mg and the dose was studied at 3 mg.

So, given that, it seems to me that there is a big margin there but, at the same time, there is also some evidence of non-linearity. So, taking all of that together, I think the part that comes into play is the clinical results and that was what Dr. Harris presented and that review did not show any big flags. But I think it is still an important thing to perhaps continue looking at and, you know, not just to overlook at this time anyway. Thank you.

DR. DUNBAR: Thank you. Are there any additional comments from the agency?

[No response]

Then, at this time I would like to thank each and every one of you for coming today to discuss Macugen, and this will be the conclusion of

the advisory committee for today.

[Whereupon, at 2:35 p.m., the proceedings were adjourned.]

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