DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPHTHALMIC DRUGS

ADVISORY COMMITTEE

NDA 21-414, Vitrase (ovine hyaluronidase for Intravitreal Injection) by ISTA Pharmaceuticals for the Treatment of Vitreous Hemorrhage

Monday, March 17, 2003

8:00 a.m.

Holiday Inn Gaithersburg
Goshen Room
Two Montgomery Village Avenue
Gaithersburg, Maryland

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Lee Simon, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. FONG: Good morning. I am Donald Fong. I am the Chair of the Subcommittee on Ophthalmic Drugs. This morning, we are going to talk about a vitreous product from ISTA Pharmaceuticals. What I would like to do is start it off by introducing everybody on the committee. Maybe we can start on my left-hand side, start with our dermatologist, Dr. Schmidt.

DR. SCHMIDT: I am Jimmy Schmidt from Houston, Texas.

DR. RINGEL: Eileen Ringel from Maine.

DR. TAN: Ming Tan, University of Maryland School of Medicine, Professor of Biostatistics.

DR. PHILLIPS: Bill Phillips from the Washington, D.C. area.

DR. WILKINSON: Pat Wilkinson from Baltimore.

DR. PULIDO: Jose Pulido from Chicago.

DR. GATES: William Gates, Nashville, Tennessee.

DR. FONG: Donald Fong. I represent Kaiser Permanent, Southern California.

DR. FEMAN: I am Steve Feman from St.

Louis University in St. Louis.

DR. DUNBAR: I'm Jennifer Dunbar from Loma Linda University in California.

DR. STEIDL: I'm Scott Steidl from the University of Maryland in Baltimore.

MS. KNUDSON: I'm Paula Knudson from Houston, Texas.

DR. HARRIS: Jennifer Harris, FDA.

DR. CHAMBERS: Wiley Chambers, Deputy Division Director for the Division of Antiinflammatory, Analgesic and Ophthalmologic Drug Products.

DR. SIMON: Lee Simon, Division Director for Analgesic, Antiinflammatory and Ophthalmologic Drug Products.

DR. BULL: Good morning. Jonca Bull, Office of Drug Evaluation IV, Director.

DR. FONG: I think we want to go back to Dr. Brown.

DR. BROWN: Jeremiah Brown from San Antonio, Texas, University of Texas Health Sciences.

DR. FONG: Kimberly, would you mind reading the Conflict of Interest Statement?

Conflict of Interest Statement

MS. TOPPER: The following announcement addresses the 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 which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting.

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

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

Thank you.

DR. FONG: I also want to point out that

Dr. Chew from the NIH will be here later one. She is stuck in traffic.

Dr. Chambers:

Introduction

DR. CHAMBERS: Thank you. I would like to take this opportunity to welcome all of the committee members and the sponsor of the New Drug Application that we are discussing and the audience for what is a not particularly frequent advisory committee based on the fact that we have tried to be as selective as possible to try and respect everybody's time and bring to the committee just those issues where we have new indications, new classes of products, something relatively new to the area of ophthalmology.

That is the case for this morning, or for today. In this particular case, we have not previously had applicants submit applications for issues involving bleeding within the eye or basically the treatment of any kind of vitreous hemorrhage, whether that is for just the treatment, whether that is for particular aspects of the indication, but any particular--this is a new indication for us.

The molecule that we are talking about is

relatively old. There is a slight wrinkle, in this particular case, in that the source is not from bovine. It is from ovine. But the molecule is otherwise relatively well-known to members of this committee.

Its use is new, and that is what we are going to primarily focus on. We will be talking about the clinical aspects of the New Drugs Application, not necessarily all of the pharm-tox or chemistry aspects, and, consequently, we will be asking for opinions on benefit-to-risk and particular aspects of this study design, the trials that were done, the results, the clinical utility.

We do not expect, whether we get yes, no or indifferent from the committee today, to have that be the final decision on whether the application is approved or not approved. There are many other aspects that go into a New Drug Application such as the chemistry and manufacturing, such as some of the pharm-tox information, other parts that we will not be discussing today.

What we are keying on is the area we believe you have expertise to help us with and that is in the area of the clinical results and the

clinical utility. We thank you for helping us with that expertise.

We are as interested in the discussion that goes on and comments that you have as any particular votes. There will be a number of votes and particular questions being asked to you, but we are just as interested in the discussion that goes along with all this and there are minutes being taken as well as a transcript being prepared which is why we ask everybody to try and use the microphones and speak as clearly as possible and identify yourself if you haven't already been introduced as you first come on to help the transcriptionist with the recordings.

At any point along, if there are any questions, please feel free to ask either the Chairman, Dr. Fong, or myself or anybody else on the FDA staff and we will try and help out and try and make things run as smoothly as possible.

Again, thank you for your time. I will turn it back over to Dr. Fong.

DR. FONG: Thank you, Wiley.

Next up is the presentation from the sponsor.

Sponsor Presentation

Introduction

DR. ANIDO: Good morning.

[Slide.]

My name is Vince Anido. I am the President and CEO of ISTA Pharmaceuticals. It is our pleasure to be here today. My role is relatively simple and that is to basically share with you our agenda for the next sixty minutes or so.

Before I do that, I would like to first of all take the opportunity to thank Dr. Bull, Dr. Simon, Dr. Chambers, Dr. Harris and the members of the FDA team for all the support and help that they have provided getting us to this point, and also Dr. Fong and the Advisory members for their time that we will be spending on this application today.

[Slide.]

ISTA is a specialty pharmaceutical company with a focus on ophthalmology.

[Slide.]

We believe, and we will be showing you data today that support the approval for the treatment of vitreous hemorrhage for our product Vitrase. It is for the treatment of vitreous hemorrhage not only to improve visual acuity but

also to facilitate the physician's ability to diagnose the underlying disease.

This will be the first pharmaceutical product approved in this particular category.

[Slide.]

Vitrase is a single injection intravitreous, highly purified ovine hyaluronidase. We have been working on this for roughly about ten years and, in that time frame, we have actually dosed up to 1,500 patients in about thirteen countries.

[Slide.]

The development history of the product pretty much spans the history of our company. We were founded in 1992 and that is when we started working on hyaluronidase for ophthalmology applications. One of the significant events for us was the fast-track designation that we received in 1998 which then allowed us to submit sections of the NDA throughout the Year 2002. That was the preclinical, clinical and the CMC sections. Obviously, that is what ha gotten us here today.

[Slide.]

The presentation for us will as follows: the clinical and the disease background will be

provided by Dr. Jack Chandler. Jack has been a consultant to ISTA for the last two years. Prior to that, he was the Past Chair and Professor of Ophthalmology at both the University of Illinois and the University of Wisconsin.

Dr. Lisa Grillone, who is our Vice President of Clinical Research and Medical Affairs, will then go through the data from the Phase II studies and show you the efficacy of the drug. Dr. Chandler will then come back and talk about the safety of the product.

After that, we will go through and have Dr. Barry Kupperman, who is Associate Professor at the University of California at Irvine in the Ophthalmology Department, and Dr. Gary Thomas, a vitreoretinal specialist in one of the largest practices in Los Angeles, will talk about the investigators' perspective. They were the lead investigators for our product in the U.S.

After that, Dr. Kirk Packo will talk about the impact of our drug on ophthalmology practice in general. Kirk is Associate Professor of Ophthalmology at Rush Presbyterian. He is the Immediate Past President of the American Society of Retina Specialists. After that, Dr. Gillone

will wrap up on conclusions.

[Slide.]

For the Q&A Section, in addition to the various presenters that we have, we have two other gentlemen, Dr. Ray Buck who is a statistical consultant for us from Cato Research, is available to answer questions as is a member of our DSMB, our Data Safety Monitoring Board, Dr. Brooks McCuen who is with Duke University.

[Slide.]

From the company available to answer questions will be, in addition to Dr. Grillone and myself, Mr. Marv Garrett who is the Vice President of Regulatory Affairs, Quality and Assurance; Bill Craig, who is a V.P. of Research and Product Development; and Kirk McMullin, who is Vice President of Operations.

[Slide.]

Now I will turn it over to Dr. Chandler.

Clinical Background

DR. CHANDLER: Ladies and gentlemen, good morning and Happy St. Patrick's Day. Fort past two years, I have been serving as a consultant for ISTA Pharmaceuticals as a member of their Clinician Advisory Board serving and working on the

preparation of this NDA, especially the safety sections, and was the Chairman of the Efficacy Evaluation Committee in the past several months.

[Slide.]

Spontaneous vitreous hemorrhages that are severe, based on one study, a prospective study, appear to occur in about 7 per 100,000 population on an annual basis. For the United States, this translates to approximately 20,000 more patients with vitreous hemorrhages entering the pool each year.

[Slide.]

The common causes, most of which lead to unilateral but not always vitreous hemorrhage, include proliferative diabetic retinopathy, posterior vitreous detachments with or without a tear or detachment, trauma, branch or central retinal vein occlusion, retinal macroaneurysm, age-related macular degeneration and subarachnoid hemorrhage.

[Slide.]

63 percent of the bilateral cases are related to proliferative diabetic retinopathy. Except for trauma and subarachnoid hemorrhages where the retina is usually normal, there is

usually preexisting retinal pathology in the other etiologies.

[Slide.]

In terms of mechanisms of vitreous hemorrhage, tear can happen in normal blood vessels, vessels from neovascularization or disease. As well, they can occur from other sites such as the choroid.

[Slide.]

The sequelae include decreases in visual acuity for the patient. For the ophthalmologist, it obstructs visualization of the posterior pole, prevents therapy of sight-threatening pathology such as retinal and choroidal neovascularization and causes, in an experimental model in nonhuman primates, at least, the blood in a large hemorrhage directly seems to cause retinal pathologic changes and electroretinographic abnormalities.

[Slide.]

Natural-history studies give us an opportunity to look at the consequences of vitreous hemorrhages. I will show you three that are very illustrative of this.

[Slide.]

A study of 85 untreated large

vitreous-hemorrhaged eyes in the United States showed that 70 percent, at three to ten years of follow up, had no better than 5/200 vision.

[Slide.]

In Spain, a similar study looking at untreated massive vitreous hemorrhages showed that, compared to baseline, 26 percent had improved at three months but 74 percent were worse or unchanged. At two years, with no treatment, half of the patients were worse than hand motion and only 21 percent were better than hand motion.

[Slide.]

The DVRS study, the diabetic retinopathy vitrectomy, which was an NEI collaborative trial, had an arm that dealt with severe vitreous hemorrhage that included 312 eyes, as you are all well aware. Half were randomized to immediate treatment after the detection and randomization was taking place for hemorrhages that were roughly at least six months in duration. Visual acuity was similar to what we have in our Phase III studies.

[Slide.]

The delayed arm is what I am talking about that gives us a look at a natural history where vitrectomy was delayed for one year. In that

group, 22 percent had the hemorrhage clear sufficiently that they didn't need the vitrectomy at one year. 11 percent had vitrectomies to deal with traction, retinal detachments. 5 percent, during that one year, became inoperable for such things as complicated retinal detachments and neovascular glaucoma.

[Slide.]

So we have currently, in our armamentarium as ophthalmologists, natural history, watchful waiting, whatever you want to talk about, where there is poor clearance, an inability to diagnose and treat the condition. While it is untreatable, there is progression of the underlying pathology and, for a vast majority of these patients, there is a poor visual outcome, not just short term but long term, as we saw in the first study.

Currently, there is no pharmaceutical treatment for vitreous hemorrhage. That is the role we are talking about today for Vitrase.

[Slide.]

On the other hand, and you are all very aware of it, is vitrectomy, a major ocular procedure. Some eyes and patients are a poor risk. It is costly. There can be serious complications.

In the DRVS, which was quite a while ago, now, they were as high as 30 to 40 percent. Given today's modern techniques and instrumentation, obviously, that rate is much lower but it is not eliminated. There are still serious complications with vitrectomy.

[Slide.]

In looking at and conceiving of where Vitrase would play a role, the following goals were set, that it would be safe, that it would speed the hemorrhage clearance, help restore visual function, allow early therapy of the underlying pathology when it was there, and it would not preclude future vitrectomy and that it would be an office procedure that was widely available.

[Slide.]

For the patient, this means, if Vitrase meets these goals, that there will be earlier diagnosis and treatment, earlier return of visual function for those with unilateral hemorrhage, and you will hear, on the videotape, a wonderful discussion of this by a patient, an improvement in their visual function. It is self evident, I think, for the patients with bilateral hemorrhages that this would be a marked help to them.

[Slide.]

As has been mentioned, Vitrase is highly purified ovine testicular hyaluronidase. It is prepared, preservative free, and it is then made up with sterile sodium chloride, the same sodium chloride that was in our saline placebo treatment arm. This is not the same, obviously, as a natural history, no treatment option, as people have now.

[Slide.]

Pharmacokinetics have been looked at in animal studies following intravitreous injection. The half-life in plasma is 49 hours. The highest concentrations are achieved in vitreous, retina and sclera. The half-life in ocular tissues is somewhere between 60 and 112 hours, roughly two to four days.

[Slide.]

In terms of the mechanisms of hyaluronidase, we know that it cleaves glycosidic bonds of hyaluron to form low-molecular-weight hyaluron. You can speculate down the rest of the way, although not fully proven, that it leads to collapse and liquification of the vitreous. It facilitates diffusion of molecules including proinflammatory chemotactic factors, that it

promotes the ingress of phagocytic cells and the egress of red blood cells and red-blood-cell breakdown products in proteins.

[Slide.]

In a schematic fashion here, and with actual clinical photos here, you can see what we conceive of as happening with treatment with Vitrase. To look at the clinical photos, this was taken the day of and just before, just prior to, Vitrase injection. This is eight days following it, and three weeks.

What you see is a large--typical of the hemorrhages that we had at the onset covering critical areas of the posterior pole and breaking up of the hemorrhage and egress of red blood cells actually happening in some patients quite rapidly, others slower. But this is what the concept of what Vitrase does following an intravitreous injection.

[Slide.]

Next, we are going to turn to talking about the Phase III trials, study design and efficacy results by Dr. Lisa Grillone.

Study Design and Efficacy

DR. GRILLONE: Thank you, Dr. Chandler,

and top of the morning to everybody here this morning. Today, I am going to provide for you efficacy results for Vitrase for the treatment of vitreous hemorrhage.

[Slide.]

Two Phase III studies were conducted, controlled clinical trials, double-masked, placebo-controlled in 131 sites in which patients were contributed to the intent-to-treat population. Overall, across twelve countries, we accumulated 1,306 patients.

You will see here that there were four doses, at least in one of the studies, in the North American study. These doses included 7.5, 55, 75 IU Vitrase compared to saline.

[Slide.]

In the Ex North American study, the 7.5 International Unit dose group was not included. For the Ex North American study, 556 patients from a total of many centers in nine countries contributed to the intent-to-treat population.

[Slide.]

In the North American study, conducted in the United States, Canada and Mexico, 750 patients contributed to the saline-controlled

intent-to-treat population study. I will also point out to you here, on the right-hand side, you see some numbers. This is the watchful waiting control study that was the initial protocol begun several years ago. This study, once it had accumulated 71 patients in which the control arm was a watchful waiting, no treatment, arm. This study was discontinued and the saline control study was reinitiated to enroll the 750 patients.

[Slide.]

Presentation today will focus on study design, efficacy measures, which I will define for you. Patient demographics and characteristics will be presented and three-month efficacy results will be presented as well. When Dr. Chandler comes back and presents safety data, that will be all of the safety included in the NDA submission for all of the patients at that time.

[Slide.]

Vitrase efficacy. Today, I am going to show you results from two controlled clinical trials that will demonstrate and confirm that we see clinical efficacy in four efficacy measures early. The first efficacy measure will be reduction in hemorrhage density; second,

improvement in best-corrected visual acuity; third, an outcome by investigator which is the surrogate success endpoint without the documentation by the investigation and, of course, the primary efficacy endpoint which was surrogate success.

You will see results in two separate trials, the arrows here indicating statistical significance, that we reached statistical significance early, at Month 1, and that that efficacy was confirmed in three of the four parameters through Month 2 and, in some cases, even as far out as Month 3.

[Slide.]

Let's begin with the eligibility criteria. Patients for this trial had to come in to the study with a hemorrhage for at least one month, but I will show you, in a minute, that actually many of these patients had hemorrhages that were much older than one month. As well, the hemorrhage had to be severe at study entry. Severity would be a Grade 3 or a 4 that would obscure visualization of the fundus, and I will define that better for you in a minute. Of course, the best-corrected visual acuity would worse than 20/200 in the study eye.

[Slide.]

Hemorrhage severity of Grade 3 or 4 in all twelve clock hours was defined for a Grade 3, for example, as a red reflex that would be visible without central retinal-vein detail posterior to the equator.

[Slide.]

Let me give you an example. This would be a nonqualifying hemorrhage because, while we see blood in the vitreous, you can see retinal detail posterior to the equator. I am not sure that you can see it here and there is a little bit of detail that you can see there.

[Slide.]

This would be a Grade 3 qualifying hemorrhage even with headlight in the fog visible. This, of course, is a Grade 4 qualifying hemorrhage.

[Slide.]

Exclusion criteria. Primarily, if the patient had a retinal detachment, ocular trauma, vitrectomy and especially if there was no light perception in either eye.

[Slide.]

For your information, this study was studied by a data safety monitoring board chaired

by Dr. Tom Fleming. Members of the board included Rick Ferris, Brooks McCuen and Alan Byrd. They conducted four interim analyses at which they evaluated both safety and efficacy. At all four interim analyses, they recommended continuation of the study.

[Slide.]

Patients were randomly assigned to receive a single intravitreous injection, a 50-microliter injection, in one eye. Three or four treatment groups, as I mentioned previously and as a reminder, the Ex North American study did not have a 7.5 IU dose group. The two doses in common to the two trials, then, were 55 and 75 versus the saline control.

[Slide.]

Efficacy measures. Reduction in vitreous-hemorrhage density. Certainly this is important to the physician because it demonstrates that there is clearance of the hemorrhage sufficiently to evaluate the underlying retinal pathology. Improvement in best-corrected visual acuity, which I will define shortly, an outcome determined by the investigator, simply the clearance of the hemorrhage with diagnosis and

treatment if required. This is the same as the surrogate success endpoint which was the original primary efficacy endpoint except that there is no requirement in the outcome here for documentation by the physician whereas the requirement, and this is an important distinction, in the surrogate success evaluation, there was a requirement for the investigator to document clearly that the laser treatment had been completed.

[Slide.]

So, while the surrogate success primary endpoint was success on or prior to Month 3, and that success being a clearance in hemorrhage sufficiently to diagnose, see the underlying retinal pathology and complete the appropriate laser treatment.

There had to be documentation that the laser treatment was completed or, for example, if no treatment was required and a fundus photograph had to be taken, there was a requirement that that fundus photograph had to be adequate. So, if you had a patient and the fundus photograph was missing or not clear, that patient would be a treatment failure in the surrogate success but a treatment success in the outcome by investigator, an

important distinction.

[Slide.]

There are several major shortcomings with the surrogate success endpoint. While it was our primary endpoint, in point of fact, there were several things that had to be taken into consideration. Data from the Phase IIB clinical trials suggested that efficacy would be met--that is clearance of the hemorrhage sufficient to diagnose and treat--by Day 56.

When these Phase III studies were planned, the sponsor thought that it would be better to extend that Day 56 time point to 90 days in order to secure that documentation from the investigator. In point of fact, you will see in a minute that we had efficacy much earlier rather than later.

[Slide.]

Again, outcome by investigator simply does not require documentation in the case report form that the treatment was completed.

[Slide.]

Reduction in hemorrhage density required that the appropriate number of clock hours, six if the patient had proliferative diabetic retinopathy, had a clearing to a Grade 0 or 1, and, for patients

who had branch retinal-vein occlusion, that clearing was appropriate in three clock hours, thus allowed the appropriate territory for laser photocoagulation.

[Slide.]

What does that look like? On the left here, a Grade 0, where you can see complete clearance, and, on the right, while you have some blood in the lower portion here, clearly there is sufficient area for the physician to do laser photocoagulation.

[Slide.]

We required this. Again, as I say, a Grade 0 or 1 and at least six clock hours, or 0 or 1 in three clock hours for those patients with branch retinal-vein occlusion.

[Slide.]

Certainly, the most important and principal efficacy endpoint is improvement in BCVA. While the surrogate success endpoint was not an endpoint that was accepted by the agency because we could not provide a complete validation for this protocol, the improvement in best-corrected visual acuity is an efficacy endpoint that is accepted. Here, we looked at a minimum of at least a

three-line improvement or 0.3 logMAR units where each letter is 0.02 logMAR units.

For those patients who were not able to read on chart, for those patients who had off-chart visual acuity--in other words, those patients who might have light perception or hand motion at study entry--and you will see, in a minute, that there were quite a number of those--we took a very conservative approach because there was no protocol-defined method for illumination and target distance and so forth.

So, because of that, we took the conservative approach that light perception to hand motion would count as a one-line improvement and hand motion to count fingers would be a second line and then count fingers to reading any letter on the chart would be the third line of improvement.

[Slide.]

Improvement in best-corrected visual acuity, of course, answers an important clinical question; is there a meaningful improvement in the patient's vision resulting from the hemorrhage density clearance. Reduction of hemorrhage density clearance of 0 or 1 clock hours--sorry.

[Slide.]

Roadmap. I will present all of the data in the following order. Study sequence will be Ex North American, then the North American study and then the two studies integrated.

[Slide.]

Let's begin with the patient demographics. You will see that there is no apparent difference between the Ex North American, North American and the Integrated dataset for the two doses in common, 55 and 75, for gender or age. Ethnicity for Caucasian, black or Asian while, in the category "other," in the North American study, 40 percent of the patients checked this category.

That represents primarily the 33 percent of the patients in the North American study that were Hispanic from the Mexican sites and several other sites with a high Hispanic population.

[Slide.]

Etiology of the baseline vitreous hemorrhage. First of all, more than 70 percent of the patients had proliferative diabetic retinopathy. 15 to 20 percent of the patients had central retinal-vein occlusion or branch retinal-vein occlusion or exudative macular degeneration, and the remainder in the other categories.

[Slide.]

I mentioned earlier, when I mentioned that vitreous hemorrhage duration had to be at least one month, that, in fact, the duration was closer to four months. You can see by the standard deviation that the range was quite high. Not only did the majority of patients have a hemorrhage duration longer than a mean of at least four months, but several, many, had a hemorrhage duration of much longer than that period of time.

[Slide.]

Baseline diabetic status. While 24 percent of the patients were nondiabetic, and I remind you that these studies were not stratified by diabetic status, more than 75 percent of the patients were diabetic at study entry. This is important because we found some interesting results in this subgroup, in the diabetic subgroup, population.

[Slide.]

Now, the off-chart visual acuity. More than 90 percent of the patients, overall, could not read one letter on chart; that is, more than 90 percent of the patients could only have vision of light perception, hand motion or count fingers at

study entry, an important point to keep in mind when we look at the changes in best-corrected visual acuity.

[Slide.]

Let's begin with the study data. Again, the original primary efficacy endpoint, surrogate success on or prior to Month 3.

[Slide.]

I would like to point out two things at this point before--I will begin the graph in a minute, but in your package, you have tables after every one of the graphs that simply describe the numbers and the absolute p-values. I will not present the tables, in the interest of time, today. I will present all the results graphically.

Furthermore, Dr. Chandler, when he presents safety data, some of the numbers that you have are just percentages and I think, in one of your earlier packets, you also have the n's go appropriately with that package. I believe you can see which slides we have hit it in the interest of time.

Let's look at the graph for a minute. I will just set this up for you. On the X axis, we have time. These will be cumulative data at Month

1, Month 2 and Month 3. On the Y axis is the proportion of patients achieving the efficacy measure in question at the moment. Saline will always be a blue line. 55 will be a yellow and 75 will be a red line.

One asterisk will mean statistical significance to less than 0.05 and two asterisks will mean significance to less than 0.005.

So if we begin with the Ex North American study, the saline group, as you see here, and the 55 IU group seen here. I will point out here that we see, again, while we did not reach statistical significance at the Month 3 time point, in fact, in this study, we reached the significance early at Month 1. Whenever you see letters enlarged in the asterisk, that denotes that there is statistical significance compared to saline.

Here is the 75 IU dose group which, while it did not meet statistical significance, certainly, by three months, was in the same trend as the 55 IU dose group.

[Slide.]

For the North American study, this is saline. Now, we have a 7.5 IU dose group in this and we see, again, at the low dose group,

significance early at Month 1, the 55 IU dose group and the 75 IU dose group, both of these doses reaching significance at Month 1 and Month 2.

So, while the significance was not reached at the Month 3 time point, we have nearly 40 percent of the patients, nevertheless, who did. But the important point here is not that we missed at three months. It is not that we got it later. Contrary, we actually reached this endpoint earlier than we anticipated.

[Slide.]

If we look at the dataset pooled for saline, and 55, which is in common, we see significance at all three time points. At 75, we see significance at Month 1.

[Slide.]

Now to the outcome by investigator. Again, the only difference here, compared to the surrogate success, is that this did not require the documentation. So that if the photograph was missing but the investigator said that there was treatment success and that they had taken the photograph, we counted this patient as a success.

[Slide.]

If we look at the Ex North American study

for saline, for the 55 IU dose group, clearly the investigators thought that there was success at Month 1, Month 2 and Month 3. For the 75 IU dose group, while we didn't reach treatment success statistical difference, we see the same trend as in the 55 IU dose group.

[Slide.]

In the North American study, for the same outcome, saline, 7.5, having a treatment effect reaching statistical significance again at all three months at 55 and 75. So, in all three dose groups in this case, we reached statistical significance for the outcome determined by investigator.

[Slide.]

In the Integrated dataset for saline and the two dose groups in common, 55 and 75, you can see that there is an early treatment effect. Again, the investigators clearly believe there was a treatment effect and that treatment effect was evident, 40 percent of the patients reaching statistical significance out to about the three-month time point.

[Slide.]

Now lets turn our attention to the

reduction in vitreous-hemorrhage density. This is the outcome that is important to the physician because it tells us how much of the hemorrhage has cleared and if sufficient amount has cleared for the underlying retinal pathology to be treated.

[Slide.]

In the Ex North American study for saline, for 55 and for 75 IU dose groups, we see a treatment effect for the 55 IU dose group early persisting through three months where we see a statistically significant difference in nearly 40 percent of the patients reaching this outcome.

[Slide.]

In the North American study, similarly for saline, first, then, 7.5, 55 and 75 IU dose groups. For the two low-dose groups, we see this treatment effect again early, at Month 1, through to Month 2, for the high-dose group, 43 percent of the patients, approximately, having a statistically significant difference in treatment effect out at three months.

[Slide.]

When we integrate the two studies for this outcome, we see, for 55, there is a statistically significant impact compared to saline both early

and for the longer time points and, as well, for the 75 IU dose group. Where we see that treatment effect, we see the reduction in hemorrhage density to nearly 40 percent of the patients by the three month time point.

[Slide.]

Now lets move to the improvement in best-corrected visual acuity. We consider this the principal efficacy measure. This gives us information about well the patient could see in the condition of a reduction in vitreous-hemorrhage density. While I will show you a minimum of a three-line improvement, I will tell you also that we have several analyses where we look at not only 15 letters improvement, how many of the patients could read 15 letters on chart and, as well, how many of the patients had 20/200 or better vision in eyes, keep in mind, that had no visual acuity except for light perception, hand motion or count fingers at study entry.

[Slide.]

So the three-line improvement, minimally, in the Ex North American study for saline, now for the 55 IU dose group, beginning with about 33 percent of the patients who had at least a

three-line improvement, reaching nearly 50 percent of the patients, 46 percent of the patients, at the three-month time point who had an improvement statistically significant difference and at least a three-line improvement by three months and the 75 IU dose group in the Ex North American study, where we consider these two numbers, while 42 percent is not statistical difference from 32 percent in the saline group, we consider these two values to be quite similar.

[Slide.]

In the North American study, for saline, for 7.5, for 55 and for 75, in all three dose groups, we see at least a three-line improvement early, one month after a single intravitreous injection, and this effect persisted through to two months for the two high-dose groups.

[Slide.]

When we look at the Integrated dataset as well, for saline, for 55 and now for 75, again, in both dose groups in the Integrated dataset, this treatment effect appears early. It is the minimal improvement in BCVA that we evaluated. Nearly 50 percent of the patients, 45 percent of the patients, maintained that treatment effect through

to Month 3.

[Slide.]

We did a confirmatory analysis for this improvement in best-corrected visual acuity. While you recall that, when I began, I said that if patients went from count fingers to reading just one letter on chart, we would count that as a one-line improvement.

We also did something called read letters as is, in which case we took the number of letters read correctly on that first line plus the distance at which the letters were read and we counted that. We calculated a logMAR unit score and called that read letters as is. So it is an absolute score.

In this case, for the integrated dataset shown here, you can see that there is a highly statistically significant difference for both doses at all three time points for those patients with read letters scored as is.

[Slide.]

What have I shown you in the Ex North American study? First, that there is an early response to Vitrase in the treatment of vitreous hemorrhage. Whether we measure it by a reduction in vitreous-hemorrhage density, statistically

significant at Month 1, improvement in best-corrected visual acuity, the same, a statistically significant difference at Month 1. Outcome by investigator and surrogate success, all statistically significant at Month 1.

At the 55 unit dose as well, this outcome, this statistically significant difference persisted through Month 2 and Month 3 for three of the four outcomes, the only difference in the surrogate being that there wasn't adequate documentation by the investigator in the case report form.

We confirmed these results in the North American study where, similarly, we see, for all four efficacy measures, an early treatment effect, earlier than we anticipated, Month 1. This treatment effect persisted for all four categories of efficacy through Month 2 and for a few of the categories, reduction in vitreous-hemorrhage density and the outcome by investigator even out to Month 3.

[Slide.]

When we look at the integrated dataset as well, we can see that there is confirmatory evidence here, when we pool the datasets, that, in all four categories, we see a statistically

significant difference not only early but one that persists and continues through three months of evaluation following such a single intravitreous injection of Vitrase.

Thank you.

[Slide.]

I would like to turn the microphone over to Dr. Chandler for the safety assessment.

Safety

DR. CHANDLER: The safety of Vitrase was determined on the basis of analyses of ophthalmologic examinations that were protocol-determined and recorded in the case report form at each visit plus adverse-event reports.

By prior agreement with the agency, systemic examinations and laboratory studies were not conducted. All of the adverse events, both systemic and ophthalmic or ocular, were coded using Medra. All coding was done without knowledge of treatment assignment.

[Slide.]

The safety population consisted of all patients who received a single intravitreous injection in the Phase III studies. In Ex North America, that included 551 patients and in, North

America, it included 740 patients from the saline controlled study.

[Slide.]

Then we had an early study which had a watchful-waiting arm in which 17 or 18 patients were in each of the four arms. I am reporting the safety data on the 53 patients from that small study that received an intravitreous injection.

So the total study population is 1,344 eyes that were injected. In none of those eyes was there injection-related endophthalmitis.

[Slide.]

This just gives you, in an integrated fashion, the follow-up that we used. Dr. Grillone earlier indicated that, at the time that this cut of data was done, all patients had reached at least the three-month visit point. This occurred at the end of September of 2001.

The mean days of follow up is quite similar. You will notice that the Vitrase 7.5, that smaller dose, had a longer, about 50 day longer, follow up as a mean in terms of patients that had at least six-months data. It was 70 percent to 75 percent. In terms of those, at that point, that had twelve-month follow up or

longer, it was 45 to 50 percent. In terms of the two higher doses, 372 patients had been looked at for at least one year.

[Slide.]

The deaths did occur in this population, as expected. You will recall that three-quarters of these patients had proliferative diabetic retinopathy and that the mean age at enrollment was 62 years. The primary causes of death were related to hypertension, cardiovascular disease and, in some cases, renal failure.

I will speak to this in just a moment, but here are the deaths across studies and integrated. Remember that this arm, I told you, had eighteen patients and there have been up to the time of the data analysis, six deaths. We have looked at all deaths in detail. They all appear to be related to their systemic underlying disease. There were none that appear in any way related to Vitrase or any other events related to the study.

[Slide.]

Looking at eyes, remember that eyes had to have at least light perception and no better than 5/200 vision at the time of entry. This gives you the picture of eyes that have progressed to no

light perception during that follow-up period I just described to you. It is not statistically significant for either the Ex North American study or the North American study. When you integrate, you can see, again keeping in mind, that this was a very small study relative to everything else, that these eyes tended to do quite well.

Again, the 7.5 Vitrase group was in North America. Again, this is an 18-patient arm here that gives you, I believe, based on the small population, a spurious result.

[Slide.]

In terms of systemic adverse events, in the Ex North American study, none of them achieved a 10 percent or greater incidence in the combined Vitrase groups that were studied.

In North America, there were four; infections and infestations, nervous-system disorders, cardiac disorders and gastrointestinal disorders. Again, you will see that there was not a statistically significant difference between the saline control patients and those that received Vitrase.

[Slide.]

In terms of discontinuation due to serious

adverse events, they were all over the map and don't appear to give us any hints about something regarding Vitrase that leads to serious adverse events that require discontinuation. We will look at that in a different way in a moment.

[Slide.]

If you look at ocular serious adverse events that achieved a 5 percent or greater incidence.

[Slide.]

In the integrated study, you find four; recurrent vitreous, or rebleed of a vitreous hemorrhage, retinal detachment, rubiosis and increased intraocular pressure.

[Slide.]

You will see that, for vitreous hemorrhage that has recurred or rebled, there is a higher incidence in the Vitrase-treated groups. It is not statistically significant and it perhaps relates to the fact that there was more efficacy in this group and clearing of hemorrhage so it was very apparent when there was a rebleed. The retinal-detachment rates are very similar. Rubiosis, as you can see, is very similar across groups. Increased intraocular pressure; again, this smaller group

with longer follow up had slightly more in it.

Most of the times, these were one or two readings that were above 23 millimeters of mercury and returned to normal. The only real big one was one patient who had preexisting primary open-angle glaucoma that was removed from the study because of the problems a few weeks after the injection.

[Slide.]

Adverse events. If you look at the Ex North American study, events that achieved a 10 percent or greater incidence and were statistically significant between saline and the Vitrase groups, it came down to a very few that did this. I want to point out, though, that, in this study, whether you were in the saline control group or the 55 or 75 treatment groups, there were frequent reports of ocular events.

[Slide.]

I think we can safely and reasonably agree that, with iritis, hyperemia and pain were typical travelers. You see that as you look at these over time. These eyes with iritis, and we will talk about this more, were not really hot eyes. The pain was not incapacitating. The hyperemia was often localized more around the injection site.

These tended to occur early.

[Slide.]

Here is the North American, same parameters; greater than 10 percent incidence and a statistical significance between the saline group and the Vitrase-treated eyes. In North America, events were reported more frequently for patients. Between 91 and 99 percent of the patients had at least one reported ocular adverse event.

[Slide.]

I think you would agree, again, that this group traveled together. Let's talk about the iritis for just a moment. The iritis tended to curve very early after the injection. It tended to not persist. It was easily managed, in many cases, with no treatment at all or with topical medications including corticosteroids, cycloplegics and, in a few cases, nonsteroidal antiinflammatory drugs.

Two down here stand out; visual acuity that was reduced, 26 percent in the saline control and in the mid-30s to upper 30s for the Vitrase-treated groups. Again, remember that these people had more clearing so there is a good chance that the reduction in V.A. which had to occur after

they had improved so you could see the reduction again, because, remember, 90 percent of these were off-chart at the start.

The vitreous-hemorrhage rebleed follows in that same vein, a little bit higher in those who received Vitrase.

[Slide.]

What can we say? I will give you some more details in a moment to support this. Vitrase administration is associated with inflammation. Iritis was frequent and was dose-dependent but it was not, for the most part, severe. We will show you some of that data in a moment. It was frequently self-limited, meaning no treatment was needed or managed with topical medications. It was also seen, as you saw, in the saline control group.

It was not a cause of many serious adverse events and there is literature evidence to support that inflammation, in fact, may help clear vitreous hemorrhage. Certainly, when you look at some of our trends of clearance or reduction in vitreous-hemorrhage density, and in eyes that had also iritis, the iritis, in almost all cases, occurred on or before the onset of vitreous-hemorrhage density reduction.

[Slide.]

Let me show you some North America data. Remember, there were more reports there. Here are the adverse events that you saw. Here is a breakdown of these adverse events by mild, moderate and severe. You can see there is, again, a dose-dependent increase in those that were referred to as severe but most of them, the vast majority of them, are in the mild to moderate.

Importantly, they were not looked at as causes of serious adverse events. Remember, I didn't show you any eyes that were discontinued from the study because of iritis. In terms of resolution, a vast majority, roughly three-fourths of them, were cleared within 30 days with or without topical treatment, and the rest of them followed soon after.

[Slide.]

Hypopyon, as you have seen in your briefing document, did occur. It was in only the Vitrase groups. Again, these eyes tended to not be hot. These eyes were eyes that were pretty easy to distinguish from an infectious endophthalmitis. It occurred most frequently in the 7.5 International Unit group. Again, as you would expect, with none

here, this was a highly statistically significant relationship.

Treatment of these, again, was managed by topical medications in the same way with prompt resolution as was the iritis.

[Slide.]

The last part of this, from looking at the North American data, is to look a little more in detail at the issue of adverse events of retinal detachment, 6 percent in the saline control group and up to 12 percent in the Vitrase-treated eyes. We looked at this carefully. If you do such things as look at retinal detachments over the first three months of study, among the groups, they are low and tend to be equal between saline and the others.

This includes retinal detachments of all types including traction retinal detachments. In fact, traction retinal detachments were a large portion of these. I have more data to back this up if you want to get into it further later.

[Slide.]

In conclusion, iritis accounted for a majority of adverse-event reports and the concomitant findings of iritis such as injection, hyperemia, were the other most common associated

adverse events. They tended to be self-limited or treated with topical medications with easy resolution. Iritis was not a common cause of a serious adverse event and did not lead to removal of eyes from the study or discontinuation.

Similarly, with hypopyon, it was infrequent and medically treatable. The no-light-perception eyes was unrelated to Vitrase treatment.

[Slide.]

Retinal-detachment rates prior to vitrectomy are low. They don't appear to be Vitrase-related. The statistics back that up. Significant SAEs tend to occur after ninety days. Remember, this is a drug with a half life in the eye of up to four days.

In summary, the safety profile of Vitrase supports human intravitreous administration of the drug for the treatment of vitreous hemorrhage.

[Slide.]

Next, I would like to call, in rotation, two of our lead clinical investigators for their perspective; first, Dr. Barry Kupperman.

Investigators' Perspective

DR. KUPPERMAN: Hello. My name is Barry

Kupperman. I am a paid consultant of ISTA and was one of the two lead national investigators, along with Gary Thomas, for the Phase III trials for Vitrase. I have no equity interest in the company.

[Slide.]

Like most retina specialists, approximately 50 percent of my patients have diabetic retinopathy and these patients are at greatest risk for vitreous hemorrhages. In evaluating patients with vitreous hemorrhage, I assess how much blood is in the eye, whether I can see into the eye well enough to diagnose and treat the underlying pathology and the impact on the patient's vision.

The strength of the efficacy data from Vitrase presented today is that there were significant improvements in all of these endpoints. A patient with severe vitreous hemorrhage is likely to have to come in monthly for three months with ultrasounds and clinical examinations, and a vitrectomy follows some 80 to 90 percent of the time.

Of greatest concern, as we are waiting for possible vitreous-hemorrhage clearance, is that the underlying pathology goes untreated, so nothing is

stopping progression. Throughout this entire time, the patient's vision and quality of life is impaired.

Additionally, our most important diagnostic tool, the B-scan ultrasound, frequently does not reveal the true extent of underlying pathology so both the patient and the physician are often literally in the dark.

I am primarily concerned about missing macular pathologies like shallow macular-traction detachments or diffuse macular edema where delays in treatment can lead to poor visual outcomes. This watchful waiting period of three months followed by the vitrectomy and post-op recovery of vision can result in a four- to five-month span where patients are functionally limited.

The most striking benefit of vitrase therapy is that it led to early significant improvement in visual acuity. As you will hear, return of useful vision, even one month earlier, is of great importance to the patient.

[Slide.]

I would like to play a tape for you of a patient who developed a vitreous hemorrhage in one eye, was enrolled by me in the Vitrase North

American study Phase III study and, as it turned out, was treated with Vitrase at the 55 IU dose.

Even though he has useful vision in his other eye, losing vision in one of his eyes from vitreous hemorrhage had a significant effect on his overall visual function.

[The tape was played for the committee.]

DR. KUPPERMAN: Dr. Thomas, the other lead investigator.

DR. THOMAS: Good morning. My name is Gary Thomas, or Edgar Thomas, as you saw on the list. My parents judged to call me something else. I was one of the two lead investigators for the Phase III trial for Vitrase with Dr. Kupperman. I obviously am a paid consultant for ISTA but I have no equity interest in the company.

I am a private-practice retina surgeon in the largest retina practice in Los Angeles. What you have seen in this patient video is a very typical scene of many of our patients There is currently only one true option for nonresolving vitreous hemorrhage and that is vitrectomy surgery.

However, before we subject a patient to a vitrectomy, we usually wait about three months which is what we consider the standard of care.

Why do we wait so long? Because vitrectomy, while certainly effective, is the most invasive surgery done in the field of ophthalmology and carries significant risk of complications including blindness, infection, retinal detachment, glaucoma and cataract.

[Slide.]

This previtrectomy period that we call watchful waiting is a complicated period for the patient and for the doctor. As you have heard from the patient in the video, he underwent this period for a period of three to four months. In that period of time, he sat home, unable to drive, work, go to the grocery store or anything by himself although, obviously, there were some things that he did try.

His experiences with severe vitreous hemorrhage are not uncommon. In fact, in my opinion, this is closer to the rule than to the exception. In this watchful-waiting period of time, there is nothing that I can do positively for the patient other than hope that the vitreous hemorrhage clears and that the underlying cause of the hemorrhage does not progressively worsen.

The watchful-waiting paradigm for managing

vitreous hemorrhage has been used for over twenty years and, despite improvements in vitrectomy instrumentation and outcomes, it is still the standard of care. Therefore, we get the same results in watchful waiting for twenty years as we do now.

[Slide.]

As a practicing physician, I feel that we need an option besides watchful waiting because watchful waiting is simply not a treatment. Rather, it is the absence of treatment which delays patients from returning to normal life and keeps the physicians from doing what they are trying to do, namely treating pathology and healing patients.

In my opinion, based on this data, Vitrase provides, for the first time, a viable option to watchful waiting for the treatment of vitreous hemorrhage and, while not perfect, would certainly be a welcome addition to our armamentarium.

Thank you.

[Slide.]

DR. CHANDLER: Next is Dr. Kirk Packo to give another view of the impact of Vitrase on ophthalmology practice.

Impact on Clinical Practice

DR. PACKO: My name is Kirk Packo. I am a vitreoretinal surgeon in Chicago. I am not a paid consultant to ISTA Pharmaceuticals nor do I have any equity interest in the company. I am being reimbursed for my expenses and time here today.

I was a local investigator as one of the 131 centers in the trial and, as mentioned, I am the Immediate Past President of the American Society of Retina Specialists, formerly the Vitreous Society, which is the largest organization of retinal specialists in the world with over 1700 members. This group makes up the vast majority of the army of physicians that deal with vitreous hemorrhage on a day-to-day basis here in the United States and my role is to speak as a foot soldier, of sorts, to that army.

Vitreous hemorrhage in the office of a retinal specialist is a common problem and, as an alternative treatment to surgery, we simply have no other treatment. But we have a need for one. Currently, in clinical practice, we approach the problem of vitreous hemorrhage with a two-armed algorithm. On one arm, we observe the patient and this choice carries with it both patient and surgeon paranoia on missing macular pathology with

instructions to go home, sleep with your head elevated and tough it out.

It carries with it considerable frustration as we have seen because the patients wants the debilitating loss of vision cleared.

The second arm is to move to vitrectomy and this carries with it the significant chance of ocular morbidity, particularly cataract formation, as well as the significant issue of cost, both financial and emotional cost. To be able to add a third arm to our algorithm I think would, indeed, be valuable.

Drs. Thomas and Kupperman have explained this watchful-waiting period as a window of about a three-to-four-month range, and I agree with that. But many times, however, surgeons need to individualize this period to a shorter window of time. A patient's visual and occupational needs, for example, may mandate a vitrectomy even within two to four weeks, particularly if that patient is monocular.

Over the past decade, I do believe that surgeons have been moving towards shorter waiting periods fostered by, perhaps, better surgical equipment and techniques. Indeed, even the DRVS

showed that performing a vitrectomy at one month may have some value in Type 1 juvenile diabetics.

I first became aware of the data on the Vitrase trial about a month ago. What impressed me is that Vitrase does work, not all the time, but it does work. When it does work, it does work quickly within that first one to two months. Adding a potential treatment alternative to surgery, to me, as a clinician, that important one to two months, I think, is very helpful.

The problem of potential disease progression during a waiting period cannot be overstated. The hemorrhagic vitreous-detachment patient, for example, a nondiabetic with a suspected tear, was often not even entered into the Vitrase trial, but this represents a particularly worrisome patient.

These patients often go to the operating room very early, within the first month, again out of paranoia or fear of missing a detachment or, at worse, will come back with a detachment. It seems to me a tragedy to see patients end up like this with potential visual loss if we did, indeed, have a pharmacologic way to clear their hemorrhage more quickly.

The provision to the vitreoretinal community of a safe, relatively noninvasive and effective treatment to get a jump start on the clearance rate to vitreous hemorrhage would be embraced by that community wholeheartedly. To have the ability to diagnose and treatment patients quicker than the natural history would certainly be worth it.

Knowing that I would be speaking to this group, over the past month, I took note of how many times I mentioned to my patients that we might have a FDA-approved drug to more rapidly clear their problem. I had that conversation ten times in the past four weeks.

If I had a vitreous hemorrhage tomorrow, I believe I certainly would want the injection myself. I hope this committee will look upon the possibility of expanding our treatment algorithm with the same excitement as does the practicing retinal specialist.

Thank you.

[Slide.]

DR. CHANDLER: For concluding remarks, Dr. Grillone will come back to the microphone.

Conclusions

DR. GRILLONE: Thank you.

[Slide.]

Ladies and gentlemen, we believe, today, we have presented to you data in two confirmatory clinical trials that a single intravitreous injection of 55 International Units of Vitrase provides the following benefits. First, and of primary importance, is the three-line improvement minimally in best-corrected visual acuity.

Second, a significant reduction in vitreous-hemorrhage density that allows the physicians that you have heard before you today and yourselves as well to be able to see and diagnose the underlying pathology, to be able to treat that underlying pathology and to help your patients.

[Slide.]

What evidence have we provided to this end? First, you have seen that that early impact on improvement in best-corrected visual acuity is seen as early as Month 1. Again, you have heard the importance of that to the physicians. As well, you have seen that that improvement in best-corrected visual acuity is maintained through three months.

As well, you have seen that the reduction in vitreous-hemorrhage density is also seen early,

again at a time point important to you and other physicians, as early as one month and significant through to three months.

[Slide.]

What are the risk-benefit assessments that you have seen today? While a single intravitreous injection of a 55 IU dose of Vitrase would provide the first pharmaceutical treatment with an early reduction in hemorrhage density and an early improvement in best-corrected visual acuity, you have seen that there is a low risk of adverse events for these patients treated with Vitrase.

With the exception of iritis, which you have also seen to be easily manageable and treatable, in some cases with topical medications if treatment, in fact, is necessary, we believe that we have provided you evidence that the benefits of Vitrase for the treatment of vitreous hemorrhage certainly outweigh the risks.

[Slide.]

At the beginning of Dr. Chandler's presentation, he presented you with a list of goals for a potential new pharmaceutical therapy. We also believe that we provided evidence to you today that Vitrase is safe with a low risk to treated

eyes, that it speeds the hemorrhage clearance and restores visual function and allows therapy of the underlying pathology, but it does not preclude use of a vitrectomy later on.

[Slide.]

Today, more than 30 years since Dr. Malcomer conducted the first vitrectomy in humans, the only alternative to vitrectomy is no treatment. You have heard about the problems with no treatment.

We ask that you carefully consider today for approval Vitrase for the treatment of vitreous hemorrhage as a new pharmaceutical therapy to provide an alternative to no treatment whatsoever for these patients to improve their visual acuity and to allow yourselves the opportunity to better and earlier diagnose and treat the underlying pathology that causes that vitreous hemorrhage.

Thank you.

DR. FONG: Thank you, Dr. Grillone.

Questions from the Committee

DR. FONG: At this point, we usually take questions to the sponsor for clarification, questions to clarify their presentation. We usually wait for discussion of the drug until the

FDA has finished their presentation. At this point, are there any questions, clarifying questions, for the sponsor? Dr. Chew

DR. CHEW: I had a question regarding the design of the study. I didn't see it in eligibility. I want to know what proportion of patients, since the majority of these cases are diabetics, what proportion had laser photocoagulation prior to their eligibility and was this balanced across all treatment groups.

DR. GRILLONE: Dr. Chew, are you asking in general how many patients had laser photocoagulation

DR. CHEW: In your integrated group. In general, sure.

DR. GRILLONE: First, I will say that, of course, only the proportion who went in with PDR, which was about 70 percent of the patients, would even be eligible for laser photocoagulation. If you give us just a minute, we will call up the appropriate slide for that.

DR. FONG: Dr. Grillone, while we are waiting, do you want to take the next question?

DR. GRILLONE: I can take another question while we are looking for that.

DR. FONG: Pat?

DR. WILKINSON: The drug seems to act relatively quickly and we have heard about--

DR. FONG: Can you introduce yourself before you--

DR. WILKINSON: Yes; I am Pat Wilkinson from Baltimore. The drug appears to act relatively quickly. We have heard about these watchful-waiting periods. I think the average entry into the program was roughly after two months of waiting. I wonder if the data were stratified to look at relatively fresh hemorrhage compared to, let's say, hemorrhage of two or three months duration.

In the application, there is a comment that the outcomes might have been even better if they had looked at more acute hemorrhages. So the question is, were the data stratified in terms of duration of hemorrhage prior to injection?

DR. GRILLONE: The data were not prestratified in terms of duration of hemorrhage at study entry. When patients entered the study, the hemorrhage was already, on average, four months old. So, by the time the hemorrhage cleared, it was, in some cases, nearly six months old.

To post stratify by hemorrhage duration meant that there was a significant cutting, of course post-stratification, and the numbers were too small, then, to draw any real conclusions because some of these patients--because there was no limit on the duration of hemorrhage, the longevity of that hemorrhage, when you did a post-stratification cut, you had many patients who had hemorrhages that were many more days older than 90 days. So the numbers got to be too small to draw any conclusions.

I have the laser-therapy slide that could be ready for Dr. Chew.

[Slide.]

What we looked at here, first of all, in the subset of patients that had PDR at study entry across the board for the integrated dataset with laser therapy conducted at Month 1, Month 2 and at Month 3. These are not cumulative. These are "at."

You can see that, as early as Month 1, because there is substantial clearing not in the saline group but, rather, in the doses, there is a higher percentage of patients who actually were able to get laser therapy when they were treated

with Vitrase and, as well, it is the same for the Month-2 time point.

DR. CHEW: I think I saw that in your datapack. I was looking for data prior to your entry into study, whether you collected that information.

DR. GRILLONE: Oh; I'm sorry.

DR. CHEW: Whether people who had proliferative disease had already been diagnosed and had treatment prior to coming in. Obviously, those of us who treat know that that happens. Even in the middle of lasering, you get patients with severe hemorrhage that come in.

So I want to know just a balance, whether there were prior laser, just in case there was a difference in your groups more than anything else.

DR. GRILLONE: I'm sorry. I understand. No; we did not that data collected. That was not built into the design of the study.

DR. FONG: Dr. Feman and then Dr. Phillips.

DR. FEMAN: I have two questions, somewhat of a surprise. Should there be any more information about visual function? Visual acuity is only one type of visual function. In most other

studies, one is concerned about other aspects of visual function like peripheral visual fields and things like that.

Yet, I didn't see anything in the packet that was supplied to us that addressed that question.

DR. GRILLONE: The studies were not designed and did not include any other examination of any other visual functions.

DR. FEMAN: Then I had a second question. In the Study 1 protocol, Vit-02, whatever its, the dosage was somewhat unexpected. There were three dosing regimens and, in it, one dose was ten times the concentration of the other. But the third was not halfway between the two. No information was given as to why that choice was made as to why not just stratifying it in half-way doses, or is that a company secret of some sort?

DR. GRILLONE: No. I am glad to share that with you today. When the Phase III studies were designed, the only available data was data from two Phase II studies that were conducted. Those Phase II studies were conducted without a saline control and with the following doses; 7.5, which you saw in the 02 study, the North American

study, as well; another dose, 37.5; and the third dose, 75.

The information from the Phase II trials on the 37.5 suggested that there was efficacy with 37.5. However, the information on the 75 IU dose group in the Phase II trials also suggested that there might be a safety issue in the amount of inflammation and hypopyon at the 75 IU dose group.

It was, actually, at the suggestion of Dr. Chambers, and we thank him for that, that we approached the 55 IU dose group to try to dose below the safety issues in the 75 IU dose group and yet achieve efficacy. That is why these two are the only studies done with the 55 IU dose group.

DR. FONG: Thank you.

Dr. Dunbar and then Dr. Steidl and Dr. Phillips, and then Dr. Tan. Dr. Dunbar?

DR. DUNBAR: You mentioned that the illumination was not controlled when visual acuity was checked. I wondered if there was a consistent protocol throughout all the study centers for checking visual acuity since, initially, the study was designed with a surrogate endpoint that was different from visual acuity.

DR. GRILLONE: I think, perhaps, I will

let Dr. Chandler answer that and speak to the best-corrected visual-acuity measurements.

DR. CHANDLER: The reference--it was probably said fast. There was not strict criteria and information for off-chart in terms of illumination. The on-chart was done like the diabetic retinopathy vitrectomy study and other diabetic retinopathy studies. That was controlled.

DR. FONG: Dr. Steidl?

DR. STEIDL: I think I have two questions. First of all, the surrogate success, and correct me if I am wrong, it is stated here that it was the primary efficacy endpoint. I was just curious, reading through these three bulletpoints, the first one laser treatment of the underlying condition completed. That makes sense.

"The visualization of the retina revealed that surgery was required." Maybe you could explain a little bit more about that because a lot of times, you don't need to see the retina to know that surgery is required. You can see a large detachment on a B-scan or, given the previous pathology, you know that there is a partial traction detachment there and maybe some proliferative disease going away and then the

hemorrhage happens.

How do you distinguish between that and the case where it is obvious that they need surgery?

DR. GRILLONE: I think, as you heard from one of the physicians, at least, the B-scans don't always provide the opportunity to completely diagnose a traction retinal detachment, for example. In some cases, once there was clearance of that hemorrhage following Vitrase, then they could see the underlying pathology and know, for example, that they might have to do a scleral buckle for tractional retinal detachment.

I can have also one of the physicians further elucidate that answer if you wish.

DR. STEIDL: If someone had a break and an obvious detachment on B-scan, you wouldn't have to wait. If someone had an obvious large traction detachment, not a subtle one, you would, again, probably not wait. If you knew that the person had maybe regressing proliferative disease just prior to the hemorrhage and you had seen the patient, you probably wouldn't wait then either. So I am just curious what this pertains to.

DR. GRILLONE: If you could see the

detachments prior to study entry, they wouldn't be eligible. If you couldn't, however, because there was too much blood in the eye, then they would be eligible. But you now would wait for the clearance to be able to see that.

I will have Dr. Kupperman come up and further expand on that answer.

DR. KUPPERMAN: Lisa is correct, in that sense. Again, anybody who had clear pathology prior to enrollment on ultrasound was excluded from the trial in terms of retinal detachment. That subset of patients was simply those that we did not diagnose any pathology based on the ultrasound but diagnosed significant pathology on clearance of vitreous hemorrhage and, once that hemorrhage was then directly visualized with indirect ophthalmoscopy, et cetera, and it was determined that, in fact, what was needed was not panorama photocoagulation but, in fact, a vitrectomy, then the endpoint was then achieved on the date that vitrectomy was done; that is, the outcome is on the day that we saw that clear enough to diagnose that a vitrectomy was necessary. The surrogate success was the date the vitrectomy was done. It was for that subset of patients whose pathology was

diagnosed purely on clearing a vitreous hemorrhage that was undetermined by ultrasound.

DR. STEIDL: So it was group where it was ambiguous as to whether they needed it and, then, upon clearing it, became clearer.

DR. KUPPERMAN: Generally, it was either ambiguous or it was not at all noted on ultrasound. Surprisingly, it was not noted on ultrasound. Then, once direct visualization allowed a determination, the pathology required a vitrectomy or other surgical procedure.

DR. STEIDL: Maybe you could just stay there for one second. The second part is a lot of times someone has a horseshoe tear and you are following them and you don't, until you really see almost 360, you are not sure that there is no break.

For the third bullet point, you accepted 180 degrees of clearing. Could you explain what that means, the 180 degrees? Is it just a little bit at the vitreous base or--

DR. KUPPERMAN: Right. Again, the requirement was a clearance of at least 180 degrees. That suggested that there was a significant amount of clearance with the hope that

we could diagnose and spot some underlying pathology such that we felt comfortable that there was no need for a surgical intervention.

We, of course, were monitoring carefully. As 180 degrees was visible, we could determine if there were superior retinal detachments and breaks although, potentially, the inferior vitreous base might be partially obscured.

DR. STEIDL: I have one more quick question.

DR. FONG: Why don't we let some of the other members ask a question and we will come back to you.

DR. STEIDL: Okay.

DR. FONG: Dr. Phillips?

DR. PHILLIPS: I note from your exclusion criteria that patients with prior vitrectomy were not included. But if patients with other intraocular surgery, especially cataract surgery, were included, what were the percentages and were they equally stratified between the treatment and control groups as patients that are pseudophakic or aphakic may clear more quickly than a phakic patient?

DR. GRILLONE: Generally, all those

patients were evenly distributed across the treatment groups. If I understand your question, you are asking if the patients who were aphakic, pseudophakic or aphakic cleared similarly whether they were aphakic at study entry, et cetera?

DR. PHILLIPS: Correct. If they were equally stratified between the saline or the watchful-waiting group versus your two or three-treatment protocols depending on the study.

DR. GRILLONE: We will be able to call a slide up for you. In the meantime, I can take a second question while they are finding the slide.

DR. FONG: Dr. Tan. Then I have a question, and then back to Drs. Steidl and Pulido.

Dr. Tan?

DR. TAN: I have two questions, actually. The first one is on efficacy. What is exactly the primary endpoint that you defined. It seems, in the briefing document, it is a little bit different from what was presented.

DR. GRILLONE: The primary efficacy endpoint in the study protocol was a surrogate success on or prior to Month 3. However, we believe that the principal-efficacy and primary-efficacy endpoint is really the improvement

in best-corrected visual acuity.

DR. TAN: Thank you. I have another clarification on the side effect. Is there data about--you say there are 30.9 percent of patients who have returned with vitreous hemorrhage for rebleed. Are there more detailed. Are there more detailed data regarding how severe, how this compared with the patients the first time, when they are first enrolled in the study?

DR. GRILLONE: Would you mind restating that question a bit?

DR. TAN: There are 30.9 percent of patients who have rebleed occurred when Vitrase was used. In the saline group, there are 21.5 percent. I just wonder what--you say rebleed. How about the severity? Do we have more detailed data about the severity of this?

DR. GRILLONE: Yes. I can show you that, for example, by severity, recurrent vitreous hemorrhage, with the slide up.

[Slide.]

This is the 02 trial, for example. There is no statistically significant difference for mild, moderate or severe rebleeds. You can see, for the mild ones, they are all running about

evenly across the four treatment groups and, while there is a certain proportion of moderate hemorrhages, similarly there is no statistical difference. Certainly, for the severe, there is no statistically significant difference with a p-value of 0.26 across the four treatment groups. This is in the 02, or North American study.

DR. TAN: Thank you.

DR. GRILLONE: I can switch, also, to the cataract slide as well. I think I am going to let Dr. Chandler address your question, Dr. Phillips, about the cataract incidence.

[Slide.]

DR. CHANDLER: On this slide, this shows you the screening status, lens status, as they came in. Almost no eyes--in fact, no eyes--were aphakic. They were pretty evenly distributed in those that happened to be--this happens to be in reduction of hemorrhage density which is a slide we have, but I can tell you, from looking at the whole database, it is almost identical. There are a few aphakic patients, very few, and they are evenly distributed. The rest are distributed just about this way between pseudophakia and phakia.

The denominator is up here of the whole

database.

DR. BROWN: So why don't those numbers add up to 100 percent?

DR. CHANDLER: There is missing baseline data on some people, so you lose that in there. This was data that was captured in ways that are not ideal for collecting complete data.

DR. FONG: Does that answer your question, Dr. Phillips?

DR. PHILLIPS: Yes.

DR. FONG: I would like to ask a question. Then back to Dr. Steidl, Dr. Pulido and Dr. Brown.

My question has to do with the presentation from Gary and Barry about the patients. I think they bring up a very important point that patients want to function better. This is also following what Dr. Feman said. I am curious to know whether you have done an analysis to look at the percentage of patients who have had improvement of vision of better than 20/40 because that would be a meaningful value, because that would be a vision that would allow patients to drive.

Also, to answer that other question, also they had talked about the need for prevention of

vitrectomy. I don't see, on any presentation, about the distribution of vitrectomy, whether vitrectomy was actually saved by the use of Vitrase. So two questions, actually; percentage of patients that had 20/40 vision or better and whether vitrectomy was reduced by the injection of Vitrase.

DR. GRILLONE: We did not do an analysis of patients who had 20/40 or better. There were several reasons for that. Then I will show you the analyses we do have.

First, of course, because 90 percent of the patients went in with off-chart visual acuity, there were so many that were severely unable to have any vision. Second, there, of course, was a proportion of patients in whom an improvement of best-corrected visual acuity would not be achievable because, perhaps, they had macular degeneration or other reasons for not being able to improve.

Nevertheless, we did do an analysis for the proportion of patients who achieved 20/200 or better which would get them out of the legally blind category in the study eye. I would like to show you that data because I think that it is an

important piece of information.

[Slide.]

This is the integrated dataset for those patients who had at least 20/200 or better, 1.2 logMAR units. You can see that, compared to saline, there is a highly statistically significant difference early, at Month 1, for these patients with more than 20 percent of the patients having gone from virtually no vision, off-chart vision, count fingers or hand motion or light perception, to having 20/200 or better.

Again, while the 7.5 dose doesn't reach statistically significance, certainly the 55 and 75, now at 30 percent by Month 2 and, at Month 3, 36 percent and 35 percent, again reaching statistical significance for 20/200 or better.

DR. FONG: Before we move off of this, I just wanted to ask whether it is possible to look not just at the integrated dataset but whether you could sort of present the data from both the U.S. and the non-U.S., that we would have a feel for what the actual numbers show.

DR. GRILLONE: Certainly. We can do that. In the meantime, I will address the vitrectomy and we will be able to show you some data on that just

to tell you that the studies were not designed to look at a reduction in incidence of vitrectomy so that there was no predesign for that.

Nevertheless, I will show you some data that will give us some information.

[Slide.]

This will be the same analysis, 20/200 or better, in the North American study again confirming what I showed you for the integrated dataset, that, for the three dose groups, where you have only 11 percent in saline, you have more than 20 percent statistically significant early at Month 1, 30 percent and more at Month 2 for the two-dose groups and, as well, while not statistically significant, still nearly 36 percent of the patients in the 55 IU dose group now have better than 20/200 vision and, in the 75 IU dose group, 38 percent of the patients reaching statistical significance in the North American study.

In a moment, we will put up the Ex North American study as well.

[Slide.]

In the Ex North American study, the time point for 55 only at Month 2 reaches statistical significance but, again, the percentages are very

similar. We have more than 30 percent of the patients at Month 2 and 37 percent of the patients at Month 3. So the same proportion of patients are achieving better than 20/200 vision, or equal to 20/200 vision.

DR. FONG: Thank you.

I think Dr. Steidl has a question. Before he asks, can I also ask whether you could, when you present the results to us, tell us whether these p-values have been corrected for multiplicity, for multiple looks for each of these results?

Dr. Steidl?

DR. STEIDL: Maybe we are all kind of interested in the same thing because, like Dr. Fong, this is a similar question. Perhaps if I knew how many achieved 20/40, this would answer it, but, in trying to determine whether I would use this on a patient, particularly since there is the risk of hypopyon and other things, I would like to know that, if I gave the Vitrase and it was successful, what the magnitude of the effect would be.

I don't know if you have evaluated that in this subgroup analysis or something, but if you gave Vitrase and they were successful, would it be

much more than, say, three lines, on average, compared to the control group when it was actually an improvement?

DR. GRILLONE: I think it would be by the data that I have just presented to you for the better than 20/200 because the three-line improvement meant that patients only got to about 1.6 LOGmar units. So the 20/200, 1.0, really represents about a six-line improvement in best-corrected visual acuity.

I think that, together with the data presented for the reduction in vitreous-hemorrhage density which also accounts for the fact that some patients are not going to be able to improve that much in visual acuity. It also tells you that there is a sort converging data, if you will, to confirm that the improvement that we see and the reduction in vitreous-hemorrhage density are both a benefit.

DR. FONG: Thank you, Dr. Steidl. We have two more questions, Dr. Pulido and Dr. Brown. I was just going to suggest that perhaps we leave the discussions about the interpretation of the results until after the FDA makes their presentation. So these should be just questions about the

clarifications of the presentation.

Dr. Pulido?

DR. PULIDO: Jose Pulido. I have a question. I didn't see any evidence in here of which patients were using Coumadin and did you stratify for the use of Coumadin. These are, obviously, very sick patients. There is a high morality rate. Was there any difference between the use of Coumadin between the patients with saline and not using saline?

DR. GRILLONE: We did not evaluate that in any way.

DR. PULIDO: The other question that I had is in regards to safety. The question is do you feel comfortable integrating the data? It appears that the study that had 40 percent Hispanics, Vit-02-08961X, had a much higher incidence of adverse events. Their retinal-detachment rates were much higher. They had a higher incidence of iritis and hypopyon as well.

Is it fair to maybe say that maybe people with more pigment, people of color, might have a higher inflammatory event with this drug than people that are not of color? Did you look at African-Americans to see if they also had a higher

rate of adverse events?

DR. GRILLONE: The design of the protocol did not collect the proportion of patients except in that category "other" and if the physician wrote in Hispanic or African American. So there wasn't an absolute check box for that category. There was the black category, but we didn't stratify in any analyses. In order to answer your hypothetical question about iris color, I will let Dr. Chandler come to the microphone.

DR. CHANDLER: The comment you raised, obviously, had peaked my interest many times while looking at the safety data. The 7.3, without a companion piece from Ex North America, gives you the biggest proportion undiluted when you look at the integrated data of patients of Hispanic background.

I think one of the interpretations that is reasonable is exactly that. The other is that a lot--remember how many of these iritis events were mild and against a brown iris, sometimes, it is hard to tell red blood cells that have leached forward from breaking up of a hemorrhage from white blood cells.

There are a number of things in my mind

that may account for that in terms of looking at just overall, from a clinical evaluation. Cells flare. They look quite similar across the board. So maybe there is more reporting. I don't know. Remember, they had a longer follow up by about fifty days in that group that show up with 7.5.

In terms of severity, going up with dose, actually, the 7.5, I think, only had one or two hypopyon patients that got higher. Those we have looked at in detail. They were not limited to people in the "other" category or Hispanic. They were represented, but it wasn't an exclusive event.

DR. FONG: Does that answer your question, Dr. Pulido?

DR. PULIDO: We can take this up later.

DR. FONG: Dr. Brown?

DR. BROWN: I also had a question concerning the safety analysis. In the retinal-detachment rate, because these patients were followed for approximately a year and all of the incidences of these events were accumulated, some of those patients would have had interventions during that year. Others would not. Do we have a feeling for what the rate was in patients who did have vitrectomy versus did not have vitrectomy?

Were they traction detachments? Any more information?

DR. CHANDLER: We have two slides that will illustrate and highlight that for you.

[Slide.]

Here is a breakdown across treatment arms of saline in the three doses for the type of detachment. You get down, importantly, rhegmatogenous was very low, traction, relatively speaking, when it was recorded. Now, these are pieces of information that are picked up in various ways off the case-report form. There were a few, as you can see, three that were listed as a combination traction rhegmatogenous detachment.

Again, keep in mind that there was more clearing for these people to have a chance to have these detected.

If I can back up a little bit to a comment, those that didn't clear on visits were scheduled and had B-scan ultrasounds so that they could be taken out and have their vitrectomy and whatever else they needed if required.

What you saw were those that cleared and you could reach the determination they needed treatment as an efficacy endpoint.

If I can have the vitrectomy slide.

[Slide.]

Here are, at the top, again, with integrated dataset, the retinal detachments. Here were those that had a retinal detachment and vitrectomy, those that had a retinal detachment after vitrectomy. You can see it way down. And retinal detachment prior to vitrectomy, very low among the groups.

So there is more, in general, or at least half that had their vitrectomy and then their retinal detachment. If you look at these in terms of time, most of the retinal detachments occurred after the Month 3 date. They were greatly delayed.

[Slide.]

Let me show you this graphically with bar graphs. For all groups, you can see that it stays under 2 percent and very low relatively, except for this early clearing group that got a chance to have detection in that early time period for 55. Then it balances out.

But there doesn't appear to be an early relationship in these first two or three months directly to Vitrase except the clearing issue that they can see it.

DR. FONG: Does that answer your question, Dr. Brown?

DR. BROWN: Yes; it does. But the one thing which would be helpful and maybe we could get this for after lunch or something, but, since the retinal detachment was different in the two studies, and this was integrated dataset, I would love to see that same data but just in the two different studies. In fact, that would be very nice to see.

DR. CHANDLER: Okay. We will do it.

DR. FONG: Paula, do you have a question?

MS. KNUDSON: Yes. Paula Knudson. I am not a physician so I may ask a very naive question. Forgive me. I was struck that the mean age of inclusion of subjects was 62 years. Yet, diabetic retinopathy, as I understand it, occurs in Type 1 diabetes who, I presume, are much younger. Was there an exclusion for younger people? What produced this 62 as a mean age?

DR. GRILLONE: There was no exclusion except that minimum age was 18 years of age. But I assume that you meant greater than 18 years of age. Nevertheless, the proportion of patients with diabetes are appearing in an older population.

I would like to have Dr. Packo address the incidence of diabetic retinopathy in all these patients.

DR. PACKO: I do think that is an excellent question and it is one that I am anxious to see this drug available for. As a clinician, when confronted with a juvenile diabetic with a dense vitreous hemorrhage, I was very reluctant to enroll that patient in this trial because I did not want to obligate them to an observational period of time after the injection of whatever. I was much more likely to move very quickly to vitreous surgery in that population.

That is why I was stressing so much that, if there is a benefit in being able to clear enough so that I can see what is happening within that first one to two months, that is very valuable in the juvenile population which, as you know, is an important diabetic population in this country.

DR. FONG: I have a question, then Dr. Chew and then Dr. Tan. My question has to do with the persistence and stability of visual-acuity gain. I think what Barry and Gary had said is that it is very important for patients to have useful vision that lasts.

So my question is--well, actually, you know what? Maybe I will defer that to the afternoon since that is not a clarification, but I will ask it now and then maybe I will re-ask it later. The question is, if you have improvement at one month and it doesn't persist, how does one justify that as being efficacy. You don't have to answer now because it is not clarification.

Let me go with Dr. Chew. You had a question?

DR. CHEW: I don't have a question.

DR. FONG: Okay. Dr. Tan?

DR. TAN: I have a clarification question. Do you have data on--the baseline data, you have presented an improvement. Do you have the raw baseline data, summary statistics, for the BCVA and the hemorrhage density?

DR. GRILLONE: We do. If I can call up one of the slides from the presentation, which are summary data, that shows that 90 percent of the patients, and we can look at this across--

[Slide.]

This is the off-chart. 95 percent of the patients had no ability to read any letters on chart in the Ex North American study. 87 percent,

or nearly 90 percent, in the North American study had no vision that was on-chart at the time of study entry. For the baseline reduction in vitreous-hemorrhage density--

[Slide.]

In the presentation and with the slide up, we can see that the duration across the treatment groups, while the minimum entry criteria was hemorrhage duration for one month, in fact, in both studies, the hemorrhage duration in each of the studies was more than four months at the time of entry into the study.

DR. FONG: Does that answer your question, Dr. Tan?

DR. GRILLONE: We may have a breakdown if you want some further detail on this.

DR. TAN: Yes; that is enough.

DR. FONG: We have a question from Dr. Dunbar and then Dr. Brown.

DR. DUNBAR: You clarified for Dr. Tan that the surrogate endpoint was the primary efficacy endpoint. I wondered if this best-corrected visual acuity as an endpoint, was that designed as a secondary endpoint or was there any prospective plan to validate the surrogate

endpoint at the beginning of the study, or was best-corrected visual acuity looked at retrospectively?

DR. GRILLONE: Let me clarify in this way. The surrogate endpoint, as the original primary efficacy endpoint, did require a validation protocol in order for the FDA to accept that surrogate endpoint.

In the absence of adequate BCVA methodology from the Phase IIB trials, we were unable to complete a validation protocol that would be adequate, based on the information we had from the Phase IIB trials in order to design an endpoint looking at improvement in best-corrected visual acuity. The information we had at the time suggested that we would need more than 1,000 patients per treatment group to have best-corrected visual acuity as a primary endpoint.

So, in the protocol, it was viewed as a principal endpoint, a secondary endpoint, but, nevertheless, the principal efficacy endpoint. It was clear that we had--without the historical information, we were able to see a statistically significant improvement in best-corrected visual acuity in the Phase III trials.

DR. FONG: Dr. Brown?

DR. BROWN: My question follows on that same issue. With the best-corrected visual acuity data, say a patient had an intervention in that first one or two months. How was the visual-acuity data handled? For that date when the decision was made, their visual acuity was recorded for that date and then no more? Or how was that handled?

DR. GRILLONE: That is also a good question. For the analyses of improvement of best-corrected visual acuity, we basically censored, although these were on Kaplan-Meier analyses. But we did censor at the time of vitrectomy or rebleed the best-corrected visual acuity. So we took the best-corrected visual acuity prior to a vitrectomy so as not to have the influence, if you will, positive if it were a vitrectomy or negative if it were a recurrent vitreous hemorrhage on the BCVA so that we could look at just the improvement as it relates to Vitrase.

DR. FONG: I have one more question and maybe we will take a break after my question if there are no other questions. Are there any more questions?

Let me ask my question and then we will take a break. My question has to do with the integrated approach. Needless to say, there are two studies. One is North America and one is outside North America. There appear to be differences in the distribution of Type 1 diabetes and ethnicity and possibly in the vitrectomy rates. I am just wondering whether you had an analysis to show that these are not substantive differences and that it is okay to combine them.

DR. GRILLONE: Actually, Dr. Fong, we do have an analysis to show that it is okay to combine these two. I would like to call one of the statisticians up to answer that question. Before I do that, I would like to, however, point out that the two studies were similarly designed. There were the same entry criteria, the same qualifications for patients. They were conducted exactly the same. The success criteria were all the same and we believe that the 55 and the 75 IU dose groups showed similar responses individually in the two studies and that it is permissible to pool the datasets.

But it is important to know that they were done and conducted identically and according to GCP

guidelines.

If I may, then I will ask Mark Knowles to come to the microphone to answer that question about the poolability of the two studies.

DR. KNOWLES: If I understood your question, you were asking about the poolability relative to the safety result; is that correct?

DR. FONG: Efficacy.

DR. KNOWLES: Oh; to the efficacy results?

DR. FONG: Yes.

DR. KNOWLES: We did do some analyses looking at that. Clearly, there are some differences between the studies and the absolute level of the response rates in the two studies. What we did is we looked at the response rate of the Vitrase groups versus saline and compared that between the two studies. I would like to show you the results of those analyses.

DR. FONG: Dr. Pulido said he wanted to hear the discussion on safety as well.

DR. KNOWLES: Okay.

[Slide.]

This slide is for the 55 versus saline group. We are comparing the dose effect of 55 versus saline and we are comparing that in the two

studies. These p-values are from a so-called Breslow-Day test. We have done it for each of the four efficacy measurements and each of the three time points. So these p-value are all nonsignificant, saying there is no statistical evidence of a difference between the two studies on the efficacy endpoints.

DR. FONG: Maybe Dr. Tan may want to comment. It seems like, to sort of determine whether the two groups can be compared, you want to sort of look at baseline differences. Are there significant baseline differences and how might they affect the poolability?

DR. KNOWLES: We did not see any significant baseline differences between the two studies, I mean in terms of efficacy results.

DR. FONG: Maybe I am not asking the question properly. Before you can look at efficacy, shouldn't you--maybe Dr. Tan, like I said, should comment. Shouldn't one look at, to see whether the two studies are similar enough to be grouped together to look at an integrated summary of efficacy?

DR. KNOWLES: Right. As far as I am aware, the only major difference between the two

studies was the racial difference at baseline.

DR. FONG: Dr. Tan?

DR. TAN: What is the rationale you want to combine these two? Don't you already have--this is two individual, independent, randomized trials.

DR. GRILLONE: Exactly. We are just providing you the data both as individual studies--we believe that each of those studies replicates evidence of efficacy from Vitrase but we also, to have a larger dataset, showed data integrated and just wanted to show for you that we have confirmed that it is statistically reasonable to combine the two studies.

But we do believe, and I should make that perfectly clear, that we have two independent controlled clinical trials in which the results are duplicated.

DR. TAN: Could you remind us, when was this, the time line, for the first and the second?

DR. GRILLONE: The first study began a little bit earlier than the second study, about in 1998. The second study started a bit later. But there were fewer patients in the Ex North American study, only 556, because we don't have one dose group in that study. So then they both ran over

basically the same period of time, both of them ending in--enrollment ending in June, 2001.

DR. TAN: Okay. Thank you.

DR. GRILLONE: So they basically overlapped except for the very beginning part because the North American trial started a little bit earlier than the Ex North American study. It was a little easier for us to get trials initiated.

DR. FONG: It is time for our break, so why don't we maybe discuss this further later on. We are going to take a twenty-minute break. I wanted to remind each of the members not to discuss the substance of the committee meeting today and to hold all discussions on line so that the transcript can be taken.

So we will reconvene at 10:20.

[Break.]

DR. FONG: We are going to reconvene our discussion on Vitrase sponsored by ISTA Pharmaceuticals. Dr. Harris is going to make the presentation on behalf of the FDA.

FDA Presentation

DR. HARRIS: Good morning.

[Slide.]

I am Jennifer Harris. I was the primary

reviewer for the NDA, for the Vitrase NDA. I am not going to repeat a lot of the information that the company has already given but what I would like to do is give you a flavor for how we looked at the data and how we came to our conclusions about the efficacy of the product.

[Slide.]

The first thing I want to clear up is how these endpoints were chosen, specifically if they are valid in this instance. I am going to talk about why it is important to correct for p-values because we were looking at so many different endpoints and how that affects the data.

I am going to go on and talk about the efficacy results for the two Phase III trials, talk a little bit about safety and then on to the conclusion.

[Slide.]

First, there were three efficacy endpoints that were submitted in the NDA package. The first one was a proposed composite which was suggested by the sponsor. The second was clearance of vitreous hemorrhage and the third was best-corrected visual acuity.

[Slide.]

Now, the proposed composite was actually not just one endpoint, as you have seen. It was a combination of three different endpoints. But, basically, success was determined if the patients cleared sufficiently to facilitate the diagnosis of the underlying retinal pathology and to provide treatment, if necessary.

[Slide.]

The three components that made up this endpoint were, one, if laser treatment was completed; two, if you were able to visualize the retina and reveal that surgery was needed and that you did complete that surgery; and, three, if you were able to visualize the macula at a minimum of 180 degrees of the vitreous base.

[Slide.]

Now I want to talk about how we viewed these endpoints and if we felt as though they were valid or not. If we look at laser treatment completed, one of the problems we had with this was that it is really ill-defined. It is variable among ophthalmologists.

For example, with patients with PDR, what is really a completed laser? Is it 1000 spots? Is it 1500 spots? Was it really defined by that point

at which that patient stabilized? Even if we could come to a consensus on a completed laser, there are still many causes of vitreous hemorrhage that would not be amenable to laser treatment

[Slide.]

The second subcategory in this composite was visualization of the retina. We believe that this is potentially a clinically meaningful endpoint if it allows for earlier diagnosis of pathology and if the timing of the diagnosis actually translates into better patient outcomes or, in other words, if the patient at which it is diagnosed, if we have already missed that window of opportunity, it would make a difference to the patients.

One problem with this is that now this patient is exposed to two invasive procedures. Not only do they get the intravitreal Vitrase injection but they will have to undergo vitrectomy.

[Slide.]

When we look at the third subcomponent in the proposed composite, which was visualization of the macula, again we believe that this could be potentially clinically meaningful, the reason being that one of the criteria is that the macula is

clear. If the macula is clear, the patient should be able to see better and that is a clinically meaningful outcome.

But what about the other 180 degrees. If you remember, this endpoint was based on only seeing 180 degrees of the vitreous base. While we agree that, if you were able to see 180 degrees and you saw a pathology that reasonably led to the vitreous hemorrhage, that that is probably the underlying cause.

But it does not negate the fact that there could still be sight-threatening pathology in the other 180 degrees.

[Slide.]

So, if we look at the composite, overall, it is potentially useful as a surrogate endpoint if it can be validated as clinically meaningful. The interpretation may be difficult based on variability--i.e., the style of practice from ophthalmologist to ophthalmologist. But you have to also remember that the underlying pathology in this situation may be missed and that patients may be exposed to two invasive procedures.

[Slide.]

So why do we call this a surrogate

endpoint. It is a surrogate endpoint because surrogate endpoints, by definition, do not directly measure how a patient feels, functions or survives, and it is used as a substitute for a clinically meaningful endpoint.

For instance, the FDA has used surrogate endpoints in the past in things like CD4 count for AIDS, cholesterol level for MI and those types of situations. But they have to be validated. They have to be validated through adequate and well-controlled trials to show that the intervention on the surrogate actually translates into a desired clinical outcome.

[Slide.]

This proposed composite was not validated. A validation plan was not completed by ISTA and, therefore, this endpoint was not accepted by the agency as a primary efficacy endpoint.

[Slide.]

Now let's move on to vitreous hemorrhage. The sponsor has already told you what the grading scale was; Grade 0 is a view of the retina and easily treatable to a dense hemorrhage of Grade 4 where there was no red reflex.

[Slide.]

In order to be defined as a success, in terms of the vitreous-hemorrhage density, that was very specific and the criteria only addressed those patients that had diabetes or vein occlusions. For PDR, you had to have at least six clock hours with a density of 0 or 1. For vein occlusions, you had to have at least three clock hours with a density grade of 0 or 1.

[Slide.]

We are not sure what this means clinically. Also, the other problem is that it will impact the trial design and impacts how we actually review the results, number one, because it only addressed the vitreous hemorrhage associated with PDR or vein occlusions and it doesn't address any of the vitreous hemorrhages that are related to retinal tears, detachments or traumas.

So, not only for this trial but in future trials, we would only be able to use this endpoint for patients who had diabetes or vein occlusions.

[Slide.]

So now we move on to improvement in best-corrected visual acuity which is the agency's acceptable and primary efficacy endpoint. It is defined as the doubling of the visual angle. An

example of this is a three-step change on the ETDRS scale or going from 20/80 to 20/40, for example, on a vision chart.

[Slide.]

This is a universally accepted endpoint. I think most ophthalmologists in the room, if they had a patient who doubled their visual angle, they would accept that as being clinically meaningful and it is the gold standard for clinical trials.

[Slide.]

So now I want to go over the data. But before we can go over all the data in the Phase III trials, we have to get an idea of what we are looking at and how we are going to evaluate it and how we are going to decide what is actually statistically significant and what isn't.

First of all, we have to realize that we are looking at a conglomeration of multiple different endpoints. First, we have three doses. In the Vit-02 study, all three doses were analyzed, 7.5, 55 and 75 units of Vitrase. There were three possible endpoints; the proposed composite, clearance of vitreous hemorrhage and best-corrected visual acuity. Then there were three different time points; Month 1, Month 2, Month 3.

So, as we look at the data, how do we decide exactly what p-value will we look at to decide if any of those results were actually significant. The reason why we have to make some corrections is because the more endpoints you have, the more chance you have to win and it increases our probability of approving a drug that may not work;

[Slide.]

You have seen this grid before. This is the grid that will be used to look at all of the results for the Phase III trials. What p-value would we have to see in each one of these blocks for us to believe that the result is real and for us not to be deceived into believing that something is significant when it really isn't.

The first correction we have to make is to go from 0.05 to 0.0459. Why is that? That is because the sponsor took a look at this data on four different occasions during the clinical trial. So, the most conservative way is to say, well, we could have gone any of nine different ways. We have three endpoints, three doses, three time points. So, at the very least, we should be looking at a p-value of 0.0051 before we believe

that anything in here is significant.

Or we can take the liberal approach, which we did, and we will say, we will just look at each endpoint individually. We will assume that the sponsor really only thought one dose will work, the 55 units. And then we will say, if it works in any of these time points, then we will take that.

So, at the very minimum, as we go through the data, we should be looking at a p-value of 0.0153 so that we will not be fooled into believing that anything that has happened is not significant.

[Slide.]

So let's go on to the data that was submitted in the NDA for the Phase III trials. This is the graph of the cumulative percentage of patients achieving a three-line improvement in best-corrected visual acuity for the Vit-02 study, or the North American study, as you all have seen; saline, 7.5 units, 55 and 75 units of Vitrase, Month 1, Month 2, Month 3.

What do we see? If you look at the 7.5 units of Vitrase, there does appear to be some efficacy early on, but this efficacy is no longer present for Month 2 or Month 3. If we look at the 55 units of Vitrase, it doesn't seem to be doing

much early on Month 1. It does appear to have some efficacy at Month 2 and this peters out again at Month 3.

If we look at the 75 units of Vitrase, it looks like there is something going on early on, which is encouraging, but, by Month 3, the results are not significant.

So this is what we saw in the Vit-02 study. Since we always need replication to make sure that what we are seeing is valid, we looked at the Vit-03 study which is the Ex North American study or the international study.

[Slide.]

Remember, this does not have the 7.5 units of Vitrase. This only looks at the 55 and 75. So what did we see? Whereas before, in the Vit-02 study, it looked as though Vitrase was doing something early on, we see that it doesn't show any statistical significance in this trial.

Then if we look at the 55 units of Vitrase, again here at Month 2, it looks promising at Month 3. So, between the Vit-02 and Vit-03 study, the only results that replicated themselves was the best-corrected visual acuity at two months for the 55 units of Vitrase.

[Slide.]

So to put a clinical perspective on this, we said, okay, there does seem to be some difference at Month 2 but what does that mean for a patient? There is a statistical difference but are the patients really seeing it. So we looked at a distribution of the best-corrected visual acuity versus the percentage of patients.

What we found is that, while there were statistical differences, there are still approximately half of the patients at Month 2 that have nonfunctional vision. What I mean by nonfunctional, I mean count fingers or worse vision. Only about 8 percent of so that have greater than or equal to 20/50, or what we were referring to earlier as the ability to be able to function and drive.

[Slide.]

So we looked at Vit-03 to see if that followed. Again, we see in the Vit-03 trials, that the results were similar, still at Month 2, there were still about 50 percent of patients who had nonfunctional vision. This is important to us because we knew that those patients would still have to go on to some additional procedure. Most

physicians would not leave them there.

[Slide.]

So we went on to our second endpoint, which was the cumulative percentage and reduction of vitreous-hemorrhage density. We look at the Vit-02 study, again, the results are sporadic but, in 7.5 IU units of Vitrase, it shows some efficacy early, peters out in Month 2 and Month 3.

For the 55 units, the only efficacy we see is at two months. For the 75 units of Vitrase, we see some efficacy early, which we were encouraged by, and that went away the Month 3. So, again, we looked at the Vit-03 study to see if it replicated.

[Slide.]

What we saw here was similar to what we saw in best-corrected visual acuity. The 75 units of Vitrase now shows no efficacy at Month 1, Month 2 and Month 3 and the only result that replicates itself in both of the trials is the 55 units of Vitrase at Month 2.

[Slide.]

So then we went on to the sponsor's primary efficacy endpoint which is this proposed composite. Remember, this was the composite which told you whether you had enough clearing to be able

to treat the underlying condition. What we saw in the 55 units of Vitrase and the 75 units of Vitrase, there was efficacy early on.

This went away by Month 3 but it was consistent in the first two months.

[Slide.]

So we wanted to look at Vit-03 just to make sure that it replicated itself and this was a real event. When we looked at the Vit-03 study, we found that there was no efficacy seen for either the 55 units of Vitrase or the 75 units of Vitrase at Month 1, Month 2 or Month 3.

[Slide.]

Since we had so many results and they seemed so sporadic to us and we really couldn't get a handle on what was going on and how do you really evaluate this data, we looked at a couple of other things to see if this could give us insight into what the problems could have been or what we would need to design future trials.

What we found is, despite the fact that these patients were enrolled in a trial for a drug that was being evaluated to treat vitreous hemorrhage, there were still approximately a quarter of the patients in each treatment group who

underwent a vitrectomy. So these were patients who the physicians felt as though they were doing bad enough that they would need a vitrectomy within the first three months.

Then that just brought in the question, and it is up for discussion, does that mean that when we look at our efficacy results, are we really seeing the patients who actually did better? Are these the worst patients, these 35 or 30 percent of patients--are these your bad players and they have been taken out of the efficacy analysis.

[Slide.]

Then we looked at the Vit-03 study and we found, again, that, while there is only about 10 to 15 percent who actually underwent vitrectomy in the first three months, it is a significant amount and it may be explained by the fact that this was Ex North American. So, does that bring into play the fact that the style of practice in America is different from that outside of the country.

[Slide.]

Then we looked at the amount of patients that were discontinued in the first three months for the Vit-02 study and we found that, within the first three months, there were approximately 10

percent, 10 to 13 percent or so, patients who were discontinued for reasons other than getting a vitrectomy.

[Slide.]

In the Vit-03 study, there were about 5 to 8 percent that were discontinued. So, in essence, when we look at these two, when we look at amount of patients who had a vitrectomy within the first three months, the amount of patients that were discontinued in the first three months, what we realized is that we have lost about 25 to 30 percent of the patients in the efficacy analysis.

So what does this mean for these results, not even these results, but in future trials, if we really need to run these trials to find out if the drug will work or not. What do we do with the fact that we are going to lose 30 percent of the patients in the first three months?

[Slide.]

Another thing that was curious to us was the fact that we had such a high death rate. In ophthalmology trials, we aren't used to people dying, or used to death rates in the 0.01 percent range.

When we saw that in the Vit-02 study and Vit-03 study, that there was a death rate of 5 percent in each study, it was of concern to us. But then, more and more, we looked at the data and we realized that, based on the population, they were an older population, they had bad, bad diabetes and the major causes of death were cardiovascular, like MI, embolus and stroke.

So we feel as though this was pretty consistent with the population and had nothing to do with Vitrase.

[Slide.]

Just a little bit about safety. The sponsor has given you data on the safety. We agree that they are similar events seen in all treatment groups and most of the events that are seen, we believe, are related to intraocular injection and not to the drug, itself.

[Slide.]

However, there are two that we do believe are drug related and that is the fact that there is an increased risk of dose-dependent sterile hypopyon and there is an increased risk of dose-dependent iritis. One thing that we were happy to see is that all of the sterile hypopyon appeared

to clear with topical steroids and cycloplegics.

[Slide.]

So, the conclusion that we came up with from the study for the efficacy was that the only efficacy that we saw for Vitrase was the fact that there was an improvement in best-corrected visual acuity at two months and there was an improvement in the clearance of vitreous hemorrhage at two months. But this efficacy was no longer present at three months.

Just to put a clinical spin on it again, while statistically it looked better at two months, 50 percent of those patients still have nonfunctional vision.

[Slide.]

Based on all that has been presented to you today, we would like the advisory committee to take all that information and to answer these questions for us.

Has sufficient evidence been submitted to support the efficacy of Vitrase for the treatment of vitreous hemorrhage? If not, what additional studies are needed to establish the efficacy of this product? Are additional analyses of the current data needed to understand the efficacy or

safety of Vitrase for the treatment of vitreous hemorrhage? Should the potential interaction, positive and/or negative, of Vitrase with current treatments for vitreous hemorrhage be evaluated? Are there adverse experiences that are of particular concern for this product? Is there a concern about the death rate observed in these studies? Do the benefits of using Vitrase outweigh the risks in the treatment of vitreous hemorrhage?

Thank you.

DR. FONG: Thank you, Dr. Harris.

Questions from the Committee

DR. FONG: Before you go, do you want to take questions from the committee?

DR. HARRIS: Yes.

DR. FONG: Dr. Pulido?

DR. PULIDO: Dr. Harris, that was a wonderful presentation. A question that I had asked the sponsors, I would like to ask you. Do you think, looking at the results of the 02 study in comparison to the 03 study, that there is a difference in adverse events in people of color as opposed to people not of color since 40 percent of the patients enrolled in the 02 were Hispanics and 80-plus percent of the patients in 03 were

Caucasians and there appears to be a higher incidence of retinal detachments and worse hypopyon formation?

DR. HARRIS: That is something that we looked at. We did not feel as though it raised a flag for us. Actually, I did not realize that that 40 percent of patients who were "other" were actually Hispanic. So I will go back and look at that data again to make sure.

DR. FONG: Dr. Brown?

DR. BROWN: You presented the data that they have in their packet regarding the cumulative incidence of vitrectomy over that first three months. So it looked like there was about a 5 percent reduction in patients needing vitrectomy in the Vitrase group, 55 units at three months. My question, was that statistically significant, that difference?

DR. FONG: Dr. Brown, what page are you referring to?

DR. BROWN: This is Page 26 in handout, the FDA handout.

DR. HARRIS: Can you repeat your question?

DR. BROWN: Yes. If you look at Table 15 on Page 26, it is the last line in that table, so

that the saline control had 24.9 percent vitrectomy versus the 55 International Units having 20.1 percent, and was that statistically significant, that difference?

DR. HARRIS: No; that wasn't. It is still of a concern to us that so many patients underwent vitrectomy within the first three months.

DR. CHAMBERS: This is Wiley Chambers. They are not statistically significant. We are not really sure what to make of it. Potentially, you can make the argument that there is 5 percent that is benefitting in this particular case. That would be good.

DR. WILKINSON: But you can spin it both ways. I don't know if--

DR. FONG: That is Dr. Wilkinson.

DR. WILKINSON: Yes; Pat Wilkinson. Sorry. You could say that the increased visualization of the fundus made the decision to proceed easier. So I think the vitrectomy outcome can be very problematic. It can good or it can be bad.

DR. CHAMBERS: This is Wiley Chambers. We absolutely agree. The point we were trying to raise along there, not just for this but

potentially for future studies, is that people are unwilling to wait for a particular point of time, is there any hope of ever seeing potential benefit from a pharmacological agent because people don't want to wait X number of months even though they knew the trial was designed, they knew they were supposed to be waiting that period of time, and that was the stated outcome, three months. People obviously felt it was in their patient's best interest not to wait that period of time. Do we have a chance of being able to study other agents if that is the typical practice pattern.

We only know that the push to do vitrectomies earlier is happening more and more as our vitrectomy procedures are getting better and better.

DR. FONG: More questions for the FDA, clarification questions? Emily

DR. CHEW: Emily Chew. I wanted to ask this question earlier because I thought maybe it would be best to ask the FDA because I wasn't certain how this was done, and that was the definition of a three-line improvement. The majority of these patients who came in had rather poor vision. They were off the chart, counting

finger, light perception, hand movement.

So it wasn't clear to me how did, say, a hand movement or LPI or counting finger--how would they achieve three-line improvement. Is that a whole line on the chart at one meter or was there gradation? They did give them one line for each of the, I think, jump from one place to another.

So, in order to be three-line improved, you had to be coming from LP to be on the chart for more than a line? And then what do you do with counting fingers? Is that two lines? That wasn't certain to me and I want to have that clarification because, in our clinical trials in the past, that is a really difficult area, dealing with poor vision. I don't know what the answer is. I think there needs to be a better way of, perhaps, quantitating these patients.

Clearly, this is a trial that needed that sort of validation of such a scale which I don't have a handle on. I know, in our trials, what we do is we say zero is their visual acuity and it sort of puts them at a disadvantage because they all have to be at zero and they have to go onto the chart for fifteen letters to say they have a three-line gain. So this is difficult and

problematic.

I just want to hear, and I thought maybe the FDA, whether you actually looked at their charts or how did they actually come up with a scale for that?

DR. CHAMBERS: This is Wiley Chambers. We also agree, we don't think there is any one good method to use. The sponsor probably has a couple of slides on exactly how that was done, if you want to pull that up. We can also talk about it. There is not a disagreement between what the sponsor used and the way the agency did.

There are actually a couple of different minor corrections, or possible different ways to go and do that. That does not change the results when you look at it, either of those two ways, as far a counting.

Either I can answer it or--Dr. Grillone, do you want to answer it?

DR. GRILLONE: I can answer it, Dr. Chambers.

DR. CHAMBERS: Okay.

DR. GRILLONE: First let me say, before we put the slide up, that, just to confirm, there was difficulty for us in that because of the vision

that the patients had. We did, just to confirm in the primary analysis that I showed for improvement in best-corrected visual acuity, if a patient started out with light perception and went then to hand motion, that would be one line. Then that same patient went to count fingers, that would be the second line.

Then if that patient went to reading any letters on-chart, that would be the third line of improvement. That would be, then, your minimum of at least three lines. For that third line, then, reading any letters, we just assumed it was 1.6 logMAR units.

In the read letters as is, if the patient read a few letters, we would to the calculation to determine the actual logMAR unit for reading those letters on-chart.

Now, if I can call up the slide.

[Slide.]

I think you can see that light perception, on the left-hand side beginning with light perception and, on the right-hand sides, both the logMAR and what we used in the Vitrase study might be. This logMAR, for example, for hand motion at 2 feet, if you knew that that was the distance, and

keep in mind that that was not standardized and defined in the protocol, but if it were, it would be three units.

At count fingers, at the same distance, it would be two and then 2800, 1.7, 2400, 1.3, and so on. In our study, because we didn't standardize, for the first three vision categories, light perception had an arbitrary logMAR unit of 2, hand motion, 1.9, count fingers, 1.8 and then 2800 was 1.7 and so on so that moving from light perception to reading any letters, then, would be at one, two, three lines of improvement in vision.

DR. CHAMBERS: This is Wiley Chambers. This we think is a more conservative method to go and use and we are willing to accept it.

DR. PULIDO: Jose Pulido. Just a question for Dr. Harris, and that is, considering that the Vitrase caused definite inflammation in comparison to the saline, do you feel comfortable that the investigators checking vision were well masked as to what the patient was taking? Do you think it might have any effects on these things like light perception versus hand motions vision?

DR. HARRIS: No; I don't think it had an impact. I think they remain masked and I don't

think that they would have been able to tell which dose of Vitrase the patients were on.

DR. FONG: Dr. Tan?

DR. TAN: This is Ming Tan. I just want to ask Dr. Harris, in the original protocol of this trial, they specifically say they are going to compare, they are going to compare three time points, one month, two months and three months?

DR. HARRIS: The original proposed primary efficacy endpoint was that composite endpoint at Month 1, 2 or 3.

DR. TAN: How about other endpoints? Did they say that the other variables or other endpoints were considered secondary?

DR. HARRIS: Yes; other endpoints were secondary. That was what was proposed by the sponsor but, because of all the issues that we had with that proposed endpoint, as we discussed, we never accepted that because the only way that we could have is if it had been validated. And that was not done.

DR. TAN: Do they plan to do three analyses for the secondary endpoints at one month, two months, three months, as well?

DR. HARRIS: Yes; they were going to look

at all three time points.

DR. TAN: That was in the original protocol?

DR. HARRIS: Yes.

DR. FONG: Donald Fong. I have a question. Going back to the discussion about the defining, giving logMAR scores to the hand motions, light perception and count fingers, I guess I want to hear a little bit more discussion about why you guys thought it was okay to accept that designation. I guess my question is twofold. One is it is very subjective in that area and, two, it is hard to ascribe a value, a functional value, in that low area.

Somebody going from light perception to even 20/800 or even seeing a couple of letters on there, or a single letter, seems to me a very, very small functional gain. So I just wanted to hear the thoughts about why you thought it was conservative to accept that.

DR. CHAMBERS: This is Wiley Chambers. The feeling was that, from a comparative perspective, going form not being able to see at all, no light perception to light perception, to go count fingers, to go to hand motion, each of those

steps, we have no good way of ascertaining how much change that is in function, how much value that is compared to a visual-acuity chart.

It has been postulated by other groups that they are more on whole-unit log units change. We have not seen other people propose lesser amounts. So, since it was the least amount that we have seen proposed by different groups, that is what we were taking. That is why I am saying it is the most conservative.

We certainly would be interested in opinions of what the proper value to assign to those values are. If there are people that can help us in the future assign values to those, we are all ears.

DR. FONG: Donald Fong. Just a follow up. I think the 5/200 sort of cutoff used in the DRS and the ETDRS was thought by the investigators, at that point, and correct me if I am wrong. It is a little bit before my time, so I would like to hear from the more senior investigators what the thinking was. But my sort of secondary recollection of that was that was thought to be sort of the last useful amount of vision, so anything less than that, it seems like wouldn't

have any functional value.

But I am curious to hear what the other committee members think.

DR. FEMAN: I can address part of that since I was involved in one of those studies even though I was probably the youngest man in the room at the time. I am Steve Feman from St. Louis University. The original reason for using 5/200 was that if a person's visual was less than 5/200, they needed assistance in ambulation. It changed their functional ability to ambulate around a room or need a seeing-eye dog. That is what that was used as a cutoff at that time.

DR. FONG: Donald Fong, again. Then Dr. Dunbar. In follow up to that, do you think vision less than that has any value--not value, functional implications?

DR. FEMAN: Vision less than, he obviously still has vision but not as functional as you would like it to be. I just don't know how to extrapolate that into a numerical value like the logMAR which is just what Dr. Wiley Chambers was talking about earlier.

DR. FONG: Dr. Dunbar?

DR. DUNBAR: I have a question about

safety. I notice one of the patients was discontinued because of elevated intraocular pressure and there was, perhaps, a slightly higher problem with elevated intraocular pressure. I wondered if there was any subgroup analysis of patients with a diagnosis of glaucoma or if those patients were excluded and if there is any reason to place warnings for these patients on the label.

DR. HARRIS: We didn't do a subgroup analysis of patients with glaucoma. There weren't that many that I can remember with glaucoma. We could surely go back and look at that again.

DR. FONG: If there are no other questions for the FDA, why don't we open it up to an open discussion--oh; one more question. Dr. Feman?

DR. FEMAN: I have one more question and it may be a different approach to this. But we talked about death rate, the observed death rate, and we talked about discontinued patient and lost-to-follow-up and serious adverse events. Has anyone thought to combine that data or is that not a statistical valid method, if one looked at a combination of lost-to-follow-up, serious adverse events and death rates and compared that in the different aspects of the trial, as a combined

number?

DR. CHAMBERS: This is Wiley Chambers. I think the amounts are relatively similar in each of the groups. All it does is drop your total number of observed patients. That is why it was being raised an issue because it makes the ultimate database for which we are making decisions as far as vitreous-hemorrhage visual acuity on that much less.

But we didn't see real differences between groups. It is just a matter of it brings the overall total number down that we are making all decisions on.

DR. FONG: How about we open it up to discussion to both the FDA and the sponsor at this point, questions to both. Maybe I will start off by asking a follow-up question with the visual acuity. What if we were to sort to take the conservative approach and assign zero to any vision that was less than one-two-hundredth, no letters read on the eye chart?

What does that do to the analysis of the three-step gain? Dr. Grillone or the FDA, has that been done, looked at?

DR. GRILLONE: Dr. Fong, I would like to

call up a slide that evaluates improvement in best-corrected visual acuity to 1.0 logMAR units which, I believe, will answer your question because this would show, of the patients--and if we could have the slide on.

[Slide.]

Of the patients who came into the study not having any vision, not being to read letters on-chart at the study entry. So we look here at the top line. Those patients with light perception, hand motion of count fingers, certainly the majority of patients across the study groups for the integrated dataset now, at Month 1--I'm sorry; LOGmar score of 1.4--we can see that there is a statistically significant difference, highly statistically significant, especially for 55 and 75 IU doses at Month 1, Month 2 and Month 3.

So this is the equivalence, said another way, of being able to read 15 letters on-chart which some have asked us about.

DR. FONG: Can I ask, again, the presentation, sort of the process of, it is hard for me to sort of see it integrated. So I am wondering whether you have that broken into the U.S. and non-U.S. and then the follow-up question

is, of these results corrected for multiplicity and, secondly, is that just a subgroup? Do you have it included for everybody?

DR. GRILLONE: Let me first show you, because you asked me about 02 and 03--so let me show you the North American study and Ex North American study for 1.4 Again, with the subgroup, however, the majority of patients, nearly 90 percent in the North American study who had off-chart vision at entry. Again, the p-values are quite statistically significant to the 0.001 and, in the 75 IU dose group, in fact, less than 0.001.

For the Month 2 time point, at 55, 0.002. And for the Month 5 at 75, also 0.001. So we believe these to be highly statistically significant although we don't have the adjustments done. In particular, you can see that p-values are quite robust, if you will.

[Slide.]

If we show, then, the Ex North American trial, which we have up on the screen now, again, as was presented by the FDA, similarly, confirmation that by Month 2, we see a statistically significant difference.

While that difference is not apparent out

to Month 3, you can see that the trend for improvement in the 55 and 75 IU group is there. Approximately 40 percent of the patients are now reading on-chart. While the difference is not significant compared to saline, of course saline would not be a treatment option in the clinic. So the same proportion of patients are able to read 15 letters on-chart out at three months, that being 40 percent of the patients reading fifteen letters on-chart.

DR. FONG: Other questions? Dr. Phillips?

DR. PHILLIPS: Bill Phillips. I was wondering, since approximately a quarter percent of the patients in the treatment group went on eventually to vitrectomy within the three months. Do you have a slide for the various indications for the vitrectomy within that time frame?

DR. GRILLONE: We don't have a slide for the various indications within that time frame. I can tell you that very few patients had hemorrhage clearance that then meant that there was a diagnosis of retinal detachment. However, that wasn't the only subgroup.

Furthermore, I would like to add, and if I could put up the slide for vitrectomy by three

months, because we have been talking about the change, and I think Dr. Chambers and Dr. Harris mentioned, that in the saline group, 20 percent of the patients had a vitrectomy while, in the 55 IU dose group, 15 percent.

Yes; that is a 5 percent difference but I think another way that we can look at that is that that is really a 20 percent relative decrease in the proportion of patients who had a vitrectomy. So, for those patients who may be at risk, for those patients who may not be a good candidate for vitrectomy, that certainly is a benefit to them.

This can compare to the relative increase in the proportion of patients who actually achieve a decrease in hemorrhage and an improvement in best-corrected visual acuity. Those relative increases fluctuate approximately between 50 upwards to 80 percent.

DR. PHILLIPS: I guess one specific question, then, would be, since we are dealing with ischemic population, either the vein occlusions or the diabetics, were there patients that developed rubiosis during the study period that had to, then, go on to vitrectomy and laser to prevent or decrease the risk of neovascular glaucoma?

DR. GRILLONE: I think I will ask Dr. Chandler to speak to the patients, especially with neovascular glaucoma and rubiosis.

DR. CHANDLER: I will have the data for you in just a moment. The brief answer is that there is no difference across the--this is the easiest to see. Let's show this one.

[Slide.]

Here is North America. You can see rubiosis is the third category, actually less than the higher doses of Vitrase. But I don't think that these are statistically meaningful across the groups.

In terms of increased ocular pressure, and these are measurements that reported as SAEs, and similar we see it with AEs, they were felt by the investigator to be important.

There was an earlier question about glaucoma. There were a few patients with glaucoma. The highest pressure that led to a serious adverse event was a patient with a pressure of 60 millimeters of mercury some fourteen days after injection in the low-dose group.

It was preexisting, primarily open-angle glaucoma, and was subsequently managed without

difficulty.

DR. FONG: Dr. Pulido?

DR. PULIDO: I have a question, but, before the question, could you leave that slide up?

DR. CHANDLER: Sure.

DR. PULIDO: Those weren't the numbers that were in Table 16. I am trying to get to Table 16 quickly here.

DR. CHANDLER: This is serious, Dr. Pulido. I think that the table you are looking at is adverse events.

DR. PULIDO: Right. But retinal detachment I would still consider serious and the numbers are different between Table 16 and these numbers up here.

DR. CHANDLER: One of the things I want to point out to you, if you are looking at tables with integrated safety data in your briefing document--

DR. PULIDO: This is not integrated.

DR. CHANDLER: Okay; the individual. We are fine, then.

DR. PULIDO: In this, saline was 5.8 percent and let's go to the 55 units. It was 10.3 percent. This was number percent of patients with ocular adverse events reported by greater than 2

percent of patients in any treatment group. Retinal detachment seems to be serious. Is there a discrepancy?

DR. CHANDLER: The difference is the opinion of the investigator at the time of whether this was a serious adverse event in their opinion or just an adverse event. Most of the traction retinal detachments were not given a serious adverse-event designation.

DR. FONG: Dr. Gates.

DR. GATES: I have one question while we are on serious adverse effects. On average, how long did the hypopyons last? How were they managed?

DR. GRILLONE: We will have a slide up for that and Dr. Chandler will address that.

DR. CHANDLER: While the slides are being called up, most of the hypopyon occurred two- to three-days after the injection. A vast majority of them were considered resolve, given a resolution date by the physician, within fourteen to twenty-one days.

Please put this up. This will be fine.

[Slide.]

So, again, these all showed up in that

very first period of time of follow up. These eyes, by the way, were not red and angry. These eyes were not particularly uncomfortable. They had some discomfort but they were not like a raging infectious adenophthalmitis kind of problem. They were treated typically with corticosteroids and cycloplegics and resolved.

By Month 3, there was just very little inflammatory response recorded, not in adverse events but even in cells in flare in the clinical ophthalmologic examinations. So these things were not lingering. They were time-specific, happened, resolved rapidly.

DR. FONG: This is Dr. Fong. Does that answer your question?

DR. GATES: Yes.

DR. FONG: Dr. Pulido and then Dr. Dunbar.

DR. PULIDO: This is directed towards Dr. Chandler. Considering that I think you were on the paper with Howard Tessler and Depak Edward about inflammation in pigmented eyes being more than inflammation in non-pigmented eyes. Again, I am still going back to this concern of mine. Did you do any experimental studies in rabbits to see if there is more inflammation in pigmented rabbit eyes

using Vitrase than in non-pigmented rabbit eyes?

DR. CHANDLER: The first part, thank you for the attribution but, unfortunately, I wasn't on the paper. I was Depak's advisor. We have done the studies on the model to look at inflammation using Dr. Beldid's pigmented iris all the way across. To the best of my knowledge, and we can check with the preclinical people, I don't think we have a comparison between a non-pigmented and pigmented eye. Everything is a pigmented. Sorry I can't elucidate that for you right now.

DR. FONG: Dr. Dunbar?

DR. DUNBAR: Jennifer Dunbar. I wondered about the safety of this drug in aphakic patients. We don't have any information at all and I think that there may be some theoretical considerations that there may be increased inflammation or increased pressure problems in these patients with this drug.

DR. FONG: Can I just follow up? What kind of theoretical--

DR. DUNBAR: The sponsor mentioned in their written package that they sent to us that the enzyme causes very small molecular-weight proteins. I wondered if these could just diffuse forward and

cause problems with trabecular meshwork. They mentioned that they suspected even that these small-molecular-weight proteins were causing inflammation that may be what is helping to decrease the vitreous hemorrhage and if these could diffuse forward that there could be more anterior-segment inflammation.

DR. GRILLONE: Dr. Chandler?

DR. CHANDLER: I share your hypothetical concern. As you can see, we did not enroll very many patients, like none, virtually, that were aphakic. So we simply can't answer that question. In theory, that is very possible.

DR. DUNBAR: If the drug was approved, do you think that there would be mention in the labeling that these are not known?

DR. FONG: Maybe we can talk about the labeling later on. Dr. Tan and then Dr. Chambers and then Dr. Phillips.

DR. TAN: I just want to follow up on the data discrepancy on the retinal detachment incidence. I think the answer that Dr. Chandler gave probably is not--causes some concern to me. Since the data for the analysis must have a freeze to the data at a certain time point, you cannot--so

the analysis, your report, should be based on one dataset that is fixed based on a certain time point.

So you cannot be different because of a physician's evaluation or opinion. So it has to be the same dataset.

DR. FONG: Can I follow up Dr. Tan's question? I guess there is a discrepancy between the numbers of retinal detachment that has been reported by the FDA and by the sponsor. I guess the answer that Dr. Chandler gave before was that some of these detachments were tractional in nature and were thought not to be an adverse event; is that correct?

DR. GRILLONE: Serious adverse events.

DR. FONG: Serious adverse events; is that correct?

DR. GRILLONE: That's correct. I would like to, at this point, distinguish there. When we are calling them serious, we are speaking to the issue of the regulatory definition of a serious adverse event.

DR. FONG: Dr. Chambers?

DR. CHAMBERS: This is Wiley Chambers. Let me first address the adverse-event thing. We

typically do not look at whether the investigators label is serious or not. We look at whether we think particular events are serious by the nature of the event.

We would consider all retinal detachments as being serious for our proposes and we would never distinguish as far as what was considered serious and not serious. We would just look at them all and look at the particular events.

But, to go back to an earlier point made by Dr. Pulido, let me just assure him that we would go through--it is routine for us to collect iris color as a surrogate of some pigmentation going on within the eye. We will go back and take a look at adverse events based on iris color to see if there is any differentiation in any of the trial.

We have not done that yet. We will go back and do that.

DR. GRILLONE: Dr. Fong, may I add, I believe a point of clarification that will help answer Dr. Pulido's question. I have consulted with my team and we believe that the table that you are referring to in that actually includes retinal detachments from both eyes; that is, retinal detachments that have occurred--and, frankly, all

of the adverse events that are reflected in both eyes.

There is another table provided in the NDA that reflects, and it is the data that Dr. Chandler has presented throughout. We only speak of the adverse events, the ocular adverse events, that occurred in the study eye.

DR. FONG: Donald Fong. I have a general question, maybe too general to answer, but I would like to hear how you interpret it. This is my question from before which is if you can't show that there is a significant difference in those patients reaching vision of 20/40 or better and you can't show a difference in reduction of vitrectomy rate, what are we offering the patient? The third part of it, the gain that you demonstrate in the first month does not persist. So what does the company say this product is offering the patients?

DR. GRILLONE: I would like to begin the answer to that question, or questions, and then, perhaps, call one of the physicians up to give their viewpoint. The company feels that we are offering to the patients the ability from a dependency on, perhaps, family members or other caretakers to the level that they can't see, for

example, the syringe gradations to give themselves injections to be able to be functional in their own homes, at the very least, because we did see a good proportion of patients that was statistically significant in both studies compared to saline that could now read 20/200 or better.

That is quite a benefit for those patients who, up until that point, were completely dependent on others just for their daily activities and, to some degree, for their own survival because they couldn't give themselves insulin injections.

So we believe that is what we are offering to the patients if this drug were approved. I would like to have Dr. Packo add to that based on his practice.

DR. PACKO: I would like take your second comment first, and that is the relationship to vitrectomy. If you look at the data particularly at one year, the incidence of vitrectomy across the board was very, very similar. So it is clear that Vitrase does not lower the need for vitrectomy in this population.

I think, as a clinician, the obvious interpretation of that is that Vitrase does not ameliorate diabetes and diabetic retinopathy. The

indication being sought here is this is not a treatment for diabetic retinopathy. What this drug appears to do, certainly and two months and with the dose suggested, is that it does clear the vitreous of hemorrhage enough to look and see what diabetic retinopathy is doing.

The vitreoretinal interface changes. The bonds that are creating traction on the retinal surface are not, in any way, being altered by Vitrase. So it basically does what it is being stated to do. It is clearing vitreous hemorrhage. The clinician looks in and still has a need to potentially perform vitrectomy and perhaps may even be doing it earlier on because we are able to diagnose these traction detachments where they were, perhaps, invisible on a subtle B-scan.

The issue on 20/40 vision is also interesting but, again, one has to address the population that makes up the majority here, and that is the diabetic. If you look at the DRVS, which was a similar study and it was a group of dense vitreous hemorrhage being randomly assigned to observation versus vitrectomy, there was a population of patients, particularly out at three years, when this was a three-year study, that about

25 percent of those patients did achieve 20/40 vision or better.

This is a three-month study, not a three-year study. Still, in the DRVS, even at six months, there was about a 20 percent group that achieved 20/40 vision at six months. But, again, that is in vitrectomy. Vitrectomy clearance of vitreous hemorrhage is certainly much more complete than Vitrase clearance, at least in the short-term.

So I think that the study was not designed nor is being suggested to really stratify out the 20/40 visions. There is data that is being presented here of 20/200 vision which, I think, does appear to have some statistical significance.

DR. FONG: My follow up; so there is agreement that this does not reduce the vitrectomy rate. Is that something that is agreed upon by the company?

DR. GRILLONE: There is a trend towards reduction in the vitrectomy rate, especially when you look at the 20 percent that occurs in the saline group versus 15 percent. It is just that the study wasn't designed to demonstrate, to a statistically significant degree--it wasn't powered to show that difference. We are simply saying that

there are various factors here that would determine whether or not getting a vitrectomy--would determine the outcome in terms of vitrectomy.

In some cases, that would be a good thing for those patients to get vitrectomy earlier because the physician could see the pathology. Because it wasn't stratified or designed that way, it is impossible to say it is a bad thing, necessarily.

DR. FONG: Dr. Steidl?

DR. STEIDL: I don't care who responds to this, if anyone wants to, but it is curiosity. I am on Page 24 of this handout, the watchful waiting. So it is just an n of 18. It really seems to have quite a different effect compared to the saline control. I am just wondering--it is hard to infer anything from that, but are we underestimating the effect of Vitrase? Can you extrapolate that at any level?

DR. HARRIS: Actually, we didn't put much credence in the watchful-waiting part of the trial because there just weren't enough patients to get any information from it.

DR. STEIDL: The reason I bring it up is because, in the real-life situation, you either

observe or you treat. Observation is actually what is significant. We are not going to inject saline into people.

DR. HARRIS: Right. But the only way that we would be able to do that is with higher numbers or looking at historical data.

DR. FONG: Dr. Chambers, I think--well, go ahead.

DR. CHAMBERS: Just responding, back to this. There are two ways to look at it. One, there are all the different problems with watchful waiting and the bias that is involved which is the other reason why we think there is difficulty in making interpretations there besides the numbers. The other is that, if we are trying to evaluate what Vitrase does, per se, that it is having to be injected and having to go in and whether there is any mechanical disturbances or any mechanical changes that happen with doing any kind of intravitreal injection, even if it is with saline, the only way to see that is to compare against the saline group.

I would absolutely agree, it is not the same as watchful waiting, but it is a better evaluation of what Vitrase, per se, is doing as a

pharmacologic agent.

DR. FONG: Dr. Phillips?

DR. PHILLIPS: Bill Phillips. Not that the study was directly designed to look at this, but, for the patients that did undergo vitrectomy, the treating physician, where they masked as to knowing whether or not that patient had had saline injection or Vitrase prior and, if not, did the Vitrase seem to, in any way, enhance or ease the Vitrase surgery?

DR. GRILLONE: The answer to your first question, were they masked, yes; they were masked and most of them actually continued to be masked to all of the treatment assignments for their patients.

In answer to your second question, because it wasn't designed into the protocol, there was nothing particularly to say whether or not--there was no data collected on ease of doing a vitrectomy, if you will, or not.

Dr. Phillips, we could, based on some Phase II trial data for the two principal investigators that are here, if you wish--that was an unmasked trial, however, so I don't know if you want to hear on their anecdotal experience with

ease of doing vitrectomy or not, but that was an unmasked, noncontrolled trial.

Yes? It was masked for dose. It was not a controlled trial; sorry.

DR. THOMAS: Gary Thomas. We were masked to the dose in the Phase II trial. So we knew the patients either go 7.5, 37.5 or 75. I have been a vitreoretinal surgeon for twenty-two years now. Those patients that ultimately came to vitrectomy, I think Barry and probably Kirk can shadow, these were really different eyes from the standpoint of vitreous. There was no, I think, difference in the vitreoretinal attachments to fibrovascular tissue but, certainly, the vitreous, itself, was almost nonexistent. These were very, very quick vitrectomies. Barry used the term, jokingly, that we just slurped it out. It just really came out very quickly. But I don't think we saw a change in the vitreoretinal attachments. I think that is probably why we were doing the vitrectomy. It did not release those surface-traction components which created recurrent hemorrhage.

DR. FONG: Dr. Brown, did you have a question?

DR. BROWN: Yes. Jeremiah Brown.

Regarding the hypothesis that increased inflammation may play a role in the efficacy of the drug, did you do any subgroup analysis to see, in your iritis population versus the ones that didn't have iritis, did they have more rapid clearance or difference in the rates?

DR. GRILLONE: We did, as a matter of fact, look at a subgroup analysis of patients who had iritis and what proportion of those patients had a reduction in hemorrhage density since we believe that is the direct relationship.

Before I call Dr. Chandler to the microphone, though, I would like to point out that this does not implicate a cause-and-effect relationship. It simply gives for you a bit of information about the relationship between iritis and reduction in hemorrhage density.

Dr. Chandler?

DR. CHANDLER: If we could have the slide up.

[Slide.]

What I am showing you here is iritis related to the reduction in hemorrhage density which, I think, gets at the question you are asking. In the patients with iritis, here are the

numbers. Here are the numbers that had reduction in vitreous-hemorrhage density, again by treatment groups. If you look, you will see that, in all cases, there is a close relationship to having iritis on or prior to the date that reduction in vitreous-hemorrhage density was recorded.

What isn't apparent to you here, but almost all of the iritis had its onset within the first few days after injection. These are, then, at time points after that. So they all, whether it was those that had iritis in the saline control or the treatment controls, had their iritis acutely and early in relationship to when they received their intravitreous injection and then here is what happened.

So, if they had reduction and there was a very close correlation with having iritis on or prior to the day where reduction in vitreous-hemorrhage density occurred, or was recorded.

DR. FONG: If you look at that the other way around, the ones who didn't get iritis, were the numbers lower?

DR. CHANDLER: No.

[Slide.]

I will show you the other way around, sort of back into what you are saying. Here are, now, the patients with reduction in vitreous-hemorrhage density. You can look at what proportion of those, then, by dose group, had iritis and which proportion of those had iritis on or before--had the reduction on or before the date of onset of the AE called iritis--on or after; I'm sorry.

DR. FONG: Does that answer your question, Dr. Brown?

DR. BROWN: Yes.

DR. FONG: I have a question and then Dr. Chambers. My question to Dr. Chambers and to the sponsor is, if we are talking about sort of a temporary gain in vision or ability to see the retina, isn't it more helpful to look at the data in time and place, like a Kaplan-Meier sort of read on this. Is it worth cutting this down further?

DR. CHAMBERS: This is Wiley Chambers. Clearly, you could do, to a set parameter, a Kaplan Meier and look at time to a particular event that you thought was useful vision. I think you are then left with a question, okay, how much time is clinically significant. Is it reduction in a day? Is it reduction in a week? Is it reduction in a

month? I am not sure that that necessarily is as helpful in this case because, in most cases, you are not seeing it earlier at Month 1. You were seeing it, basically, at Month 2.

The reoccurring finding they keep seeing is a bettering in Month 2 in the 55 group. I think the question, then, remains is that good, bad or indifferent.

DR. GRILLONE: Dr. Fong, may I add to that, if Dr. Chambers is finished. Two things. First of all, while we are not seeing a statistically significant difference at Month 3, we are still seeing a high proportion of patients in the Vitrase-treated groups who do have a three-line improvement. I think it is important in the context that, as we have mentioned before, that patients are not likely to get treated with saline. That is not something we would do.

So the fact remains, nevertheless, that 40 to 45 percent of the patients treated with Vitrase, even at three months, do have a three-line improvement.

The second thing is, with regard to doing a Kaplan-Meier, if I may call up the statisticians, because we did think about this. But there is a

statistical reason better described by the statisticians of why it is not appropriate to do a Kaplan-Meier in this case.

DR. BUCK: Raymond Buck, Cato Research. Given the way the that data were collected, there are actually collected at very discrete time points. So a time-to-event analysis, which was more a live-table analysis, could be done rather than a straight Kaplan-Meier and we do have that if you wanted to see it.

DR. FONG: If you have it, let's look at it. This is Donald Fong.

DR. BUCK: This doesn't have the appearance of the usual Kaplan-Meier curve, but I think it shows you the survival distribution.

[Slide.]

Again, the blue line is saline, green, 7.5. Again, we are plotting the probability of survival rather than starting at 1 and coming down. We are from 0 and going up.

DR. FONG: Did you test this?

DR. BUCK: There were formal tests on improvement, time to BCVA improvement. I am not recalling the p-values exactly. I am looking at my colleagues now to see if they can provide you with

that answer.

DR. FONG: This is just a side administrative note, since we are ahead of schedule. I am wondering how the group thinks about taking an earlier lunch and reconvening earlier. Dr. Chambers?

DR. CHAMBERS: This is Wiley Chambers. I think that was potentially the plan. We have an open public forum, meeting that it needs to more or less stay fairly close to being on time. So I think our expectation would be to go ahead and take an early lunch and then come back for both the open public forum as well as, then, the rest of the discussion.

I commend the Chair for staying ahead of schedule.

DR. FONG: I commend the sponsor and the FDA. Is there any opposition to taking an earlier lunch? Can we reconvene maybe at 12:45? An hour and fifteen for lunch; is that okay? Let me remind, again, the committee staff not to discuss the substance of this committee meeting outside of the transcript that is in process here.

[Whereupon, at 11:30 a.m., the proceedings were recessed to be resumed at 12:45 p.m.]

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

[12:50 p.m.]

DR. FONG: We are going to reconvene the Subcommittee of the Ophthalmic Drug Advisory Committee discussing the NDA for Vitrase sponsored by ISTA Pharmaceuticals.

Committee Discussion

What I would like to do is have an open discussion with the sponsor and the FDA. Then, at 1 o'clock, we will break for an open public hearing in case there are public members who want to speak up.

Are there questions for the sponsor or the FDA? Dr. Brown?

DR. BROWN: Just the one thing that was left over from this morning. Do you have that data now on the retinal detachment related to vitrectomy which ones had it and did not but separated between the different studies. So the data that was shown was the combined integrated, but pre- or post-vitrectomy retinal-detachment rates.

DR. GRILLONE: Dr. Chandler?

DR. CHANDLER: If I may have the first slide.

[Slide.]

This is the North American study showing, in the same format that you saw with the integrated study, total RDs. These are throughout the total follow up. These are not through Month 3 or anything. They are the total that had a retinal detachment and vitrectomy recorded.

These are the portion, or the whole numbers, whatever you want of retinal detachment after the vitrectomy as opposed to before. I think you can see the numbers. It is roughly 50 percent, in each group, had their retinal detachment after a vitrectomy as opposed to before.

DR. FONG: Dr. Pulido?

DR. PULIDO: Jose Pulido. Just a point of clarification. Again, before, when we were talking about Table 16, you told us this was ocular adverse events that were--and this is North America. But those numbers are exactly the numbers in Table 16. Yet, you were telling me that Table 16 was either eye. Is this the affected eye and are the numbers, then, in Table 16 of the affected eye?

DR. CHANDLER: I'm sorry; I don't remember what Table 16 is in your thing, but if it says that it is--

DR. PULIDO: It is the exact same numbers

and yet you told me before it wasn't, it was either eye.

DR. CHANDLER: In the integrated reports of safety in here, it is both eyes. In the individual studies in your document, these are study eye.

DR. PULIDO: This is--

DR. CHANDLER: Study eye.

DR. PULIDO: So then there were eighteen retinal detachments in the Vitrase-treated group with 55 International Units in the North America group in the study eye; correct?

DR. CHANDLER: Correct.

DR. PULIDO: That is 10.3 percent versus 5.8 percent for the saline-treated group.

DR. CHANDLER: That is correct.

DR. PULIDO: So, is that statistically significant?

DR. CHANDLER: No; it is not.

DR. PULIDO: Okay.

DR. CHANDLER: Let's show this slide, just to give you another look at things.

[Slide.]

Here was time-to-diagnosis of the retinal detachments. Again, this is North America showing

you retinal detachments in the study eye. The main point here is that you see very few retinal detachments reported as adverse events in the first month following an intravitreous injection. You see that it progressively increases and, as you get to greater than three months is where you see the bulk of them for each group. So they tend to be late.

Would you like to see the same data for Ex North America?

[Slide.]

Here is Ex North America, giving you the same picture. Those that were detected in 30 days or less, 31 to 60, again 90 and greater than 90. Again, you will see that the majority of them tend to show up in this greater than 90. Here you see a good example of something cleared, in all likelihood, enough to make the diagnosis and then report the adverse event of a retinal detachment because there was clearing.

DR. BROWN: That is really helpful data. I think we should get that on paper, the last few slides that you have shown. That is very helpful.

The other part of it was traction versus rhegmatogenous and you showed us this morning the

integrated data. Do you have that separated?

DR. CHANDLER: Bear with me just a moment please.

DR. FONG: Dr. Steidl has a question.

DR. STEIDL: Can I just ask a question? You said what of those had cleared? I didn't follow that.

DR. CHANDLER: I said, in the Vitrase-treated group, there tended to be clearing, as you have seen, more frequently, often uncovering a detachment. So you got a chance to see it earlier.

DR. STEIDL: What percent would you say?

DR. CHANDLER: Well, clearing in the first month went in the range of 25 to--roughly 25 percent of them cleared.

DR. STEIDL: Of the ones that ended up with detachments cleared enough to see the detachment?

DR. CHANDLER: Yes.

Let's bring up this next slide.

[Slide.]

This is Vit-02, as you have been hearing. That is North America. Here is the breakdown by traction, retinal detachments in this group. You

can see that it was in this proportion, more traction retinal detachments, probably again a relationship to more clearing, so you had a better chance to see it.

Here was rhegmatogenous, unspecified, since in the case reports, some people did not record whether it was rhegmatogenous or traction or a combination.

DR. BROWN: That is helpful. So, then, in the interpretation of it and from your standpoint, you are saying that probably it helps us see it better. The other possibility is that the increased inflammation creates more traction as a possibility. Have you thought about that or has that been looked at in animal models or anything like that?

DR. CHANDLER: We have not looked at an animal model. Certainly, we have thought about it. The way the numbers come over time, if it was looking at traction, we don't see a separation of this tendency in time between saline and Vitrase. I would think you would start to see those separate as you get out to three months, and we don't see that.

DR. FONG: Dr. Feman and then Dr. Steidl.

DR. CHANDLER: I didn't know if he wanted to also see separately the Ex North America or not. If you don't mind, Dr. Fong.

[Slide.]

Here is the 03 again, same setup. This is Ex North America traction. Here you see that it is pretty much straight across. Only one reported rhegmatogenous, and you can see a majority of them ended up unspecified. There was poor recording of whether it was traction, rhegmatogenous, combination or unspecified. But, again, I think you see this leaning toward that allow these were traction retinal detachments.

DR. PULIDO: Just a point of clarification on this. If your hypothesis is correct that it just helps you see it better, then you would have had, basically--in the two groups, it would have had the same numbers.

DR. CHANDLER: We didn't have the same amount of clearing, Dr. Pulido, in the two studies at the same periods of time.

DR. FONG: Dr. Feman?

DR. FEMAN: My concern is about the retinal toxicity of this agent that you are injecting. For example, if a person has had a

previous vitrectomy and, therefore, he does not have, or she does not have, the vitreous that she was born with and this agent was injected into the vitreous cavity, what do we know about retinal responses to this agent, to an eye that no longer has vitreous?

DR. GRILLONE: We don't have any data with regard to eyes that don't have any vitreous.

DR. FEMAN: There are no animal studies of any kind that would address this?

DR. GRILLONE: Nothing in animals where we have removed the vitreous and then looked at retinal toxicity. I would like to have Dr. Brooks McCuen who is a member of our DSMB.

DR. McCUEN: There really would be no indication for ever using Vitrase in a post-vitrectomy eye because there was no rationale for how it would work. The vitreous was already liquified and there is nothing to break up so there would be absolutely no use for using Vitrase in that situation.

DR. FEMAN: I know that and you know that, but I don't know if every doctor in the United States would know that when this is commercially available.

DR. FONG: It is hard to solve that problem.

Dr. Steidl?

DR. STEIDL: Just a protocol question. You are saying that three-quarters of the eye, at the time of detachment, would not have clearing. How are those categorized? Were those continued failures then, because that would not meet your primary efficacy endpoint.

DR. GRILLONE: Certainly, if they didn't have a reduction in hemorrhage density, then they wouldn't be counted as having a success. But I am not quite sure that that is what Dr. Chandler was exactly referring to. I think he was just talking about, in a subset of patients, the relationship between retinal detachment and clearing.

DR. STEIDL: I am just trying to understand how you are defining this second bullet point of the efficacy endpoints. "Visualization of the retina revealed that the surgery was required." So, in that case, the surgery was required but, if you couldn't visualize the retina, then that would not be--

DR. GRILLONE: Correct. In that case, if you couldn't visualize the retina and if there was

no documentation that surgery was completed, then that would be a treatment failure for that patient. This is where the distinction in the surrogate endpoint compared to the outcome by investigator is important because, to be a success in the surrogate endpoint, for that particular one, for example, we would have had to have had documentation on a case-report form that that surgery was completed within the window.

On the other hand, if the physician simply checked Box No. 2 and said, "Yes; the hemorrhage has cleared. I will do surgery," but either the surgery didn't get completed within the window or there was some failure to document that the surgery was done, in the outcome by investigator, that would be a treatment success. So those two endpoints are really one and the same. It is just one not requiring the absolute documentation. But the outcome by investigator, it is important to keep in mind, is really the same as a surrogate-endpoint success.

Have I made that clear to the panel?

DR. FONG: At this point, let's take a break in the general discussion and open the floor up for comments from the public.

Open Public Hearing

DR. FONG: Are there any speakers from the public who would like to make a comment to the committee? I don't see any. Does anybody see any? If not, let's resume our discussion.

Committee Discussion

DR. FONG: Maybe I will start with a question for Dr. Tan. The FDA has presented to us issues with multiplicity and the choice of p-value. Do you agree with that, that there are very few endpoints that are statistically significant?

DR. TAN: Yes. I think I do. That is why I asked what was in the original protocol because the primary endpoint now were the secondary endpoints in the original protocol. When you make inference based on your efficacy on a secondary endpoint, you should really adjust it for the multiple comparisons. So the cutoff should be adjusted.

DR. FONG: Donald Fong. You agree with the adjustment proposed by the FDA?

DR. TAN: Yes.

DR. FONG: Maybe I will just start off the discussion also again talking about the surrogate endpoint that has been proposed by the company.

How do people feel about this endpoint that is proposed, laser treatment or visualization of the retina revealed the surgery was required or visualization of the macula with a 180 degrees of vitreous base.

Observations about that? Emily

DR. CHEW: I think that is a difficult one to validate. Unless it is validated, I think it is hard to use as an endpoint. Obviously, there are many issues involved that we, as clinicians every day, see. As a clinical trial, I think that is a difficult one. It is not standardized. It is not validated. People have different bars as to what they want to do surgery. I think that is a difficult one to actually use.

The only hard endpoint we really have is really visual acuity at this point. What I would like to see, then, perhaps in that composite might have been some patient function aspect that might have been incorporated in there more than what it has got at this point. This is all, really, what the physician decides based on this and I think function has to come in there more.

I think that is where I would put this.

DR. FONG: Dr. Pulido?

DR. PULIDO: Jose Pulido. I agree with Emily but, on the other hand, as one can see from the patients this was used in, this wasn't used in your Type 1 diabetics. This was used in those patients that were probably so sick that they couldn't even undergo a vitrectomy in a lot of cases. There is a huge mortality rate in the group of patients that were picked.

So, thinking about whether I would use this medication or not, I think it would be reasonable in those patients that are so ill that I wouldn't want to take them to vitrectomy, I would want to try something, an alterative treatment.

Although it is a bad endpoint, I think it is not an unreasonable endpoint to consider from a clinical point of view.

DR. FONG: Dr. Wilkinson?

DR. WILKINSON: I would agree. These patients are incredibly difficult to manage. It is no surprise that this is not a perfect statistical analysis with clean outcomes. I don't know. I hate to be a statistical nihilist, but, with all due respect to these patients, I think the critical issue here is that the view in is more important than the view out.

No matter what the p-values are, it is pretty clear that, from 50 percent to 100 percent more patients experience clearing with an injection than with saline, with an injection of the drug than with saline. So something is happening.

The two things that are happening is we are getting some inflammation and we are getting some clearing of the vitreous gel. Don, you mentioned what do we offer the patient. The key to managing these patients is to control the retinopathy. As Dr. Harris noted, the amount of laser burns that a person needs to control retinopathy varies tremendously from many hundred to many thousand.

But the key to managing these patients is to be able to see what is going on, what is the status of the vitreoretinal interface. I think if a sufficient number of people seem to be having something happen that can enhance their outcome that this type of surrogate analysis, it is not clean. It is not--Emily stated it very, very well, but I think it is clinically meaningful, as Jose just said.

DR. FONG: Anybody else? Observations? Dr. Tan?

DR. TAN: Statistically, it comes forward here that the analysis is just saying if this is going to be used in a larger patient population, that is why I want to consider the Type 1 error.

DR. FONG: Tell me that again?

DR. TAN: That is the point of condidering the Type 1 error is that once the product is going to be used in a larger patient population, that is why we want to consider the Type 1 error here.

DR. FONG: Maybe I can just sort of continue this ongoing discussion. It sounds like people like the proposed composite even though it hasn't been validated. The next issue is has the company showed that that has been effective, that it actually does do any clearing. What does Dr. Tan think of this? What do you think of the efficacy based on the proposed outcomes?

DR. TAN: This is--the company--

DR. FONG: Why don't I come back to you. Why don't you take a look. I would like to get your read on it. Other observations from committee members, general observations? Dr. Steidl?

DR. STEIDL: Maybe I am saying the obvious but just with comment to the composite index, where I am having difficulty with the visualization of

the retina as one of the endpoints is that these conditions are all a little different. If you suspected a peripheral break, you might need to see 360. That is not really included in here. Where, if you are suspecting vein occlusion, you may only need to see a small part of the eye and may only need to treat an area.

So the potential, again--some things could be managed by B-scan that could develop where you couldn't see it. So it is kind of hard for me to understand how you lump all these different conditions together with this endpoint. At the same time, I think it is valuable in concept.

DR. FONG: This is Donald Fong, again. I sort of agree with what you have said and I agree with what Pat and Jose have said, and that is it is important--it would be helpful to be able to see the retina to see if there is any pathology. But that is one step away from the preservation of vision or improvement of vision.

What may be missing, and what Scott pointed out, is sort of the connection between identifying these things at one month and the ultimate visual prognosis. For example, if you diagnosed a detachment that is already there, the

macula that has been off and so forth, it may not make a difference that you have picked this up at two months versus three months.

So that connection may not be present. I am wondering if people agree with that. Thoughts on that, the connection between diagnosing things earlier and the ultimate visual outcome. Dr. Phillips?

DR. PHILLIPS: Bill Phillips. I think some of the things, we don't really have sort of a standardized protocol in this study for the B-scan, but a lot of the "traction retinal detachments," it is not broken down into whether it is macular or extramacular.

Certainly, if it is a nasal extramacular detachment, you could watch longer than you would want to watch a macular detachment whenever you find it. The other thing I was a little concerned about, just as Scott and other people have pointed out, to say that there is clearing to see 180 degrees, you could missing something that way. Also saying that you are getting clearing enough to do "laser treatment."

Depending on how much ischemia there is, you may put in some laser but not really stop the

process. If you are not stopping the ongoing process, you are not really treating the patient. I think what Dr. Feman was saying earlier, too, vitreoretinal specialists would probably use this in a different way than a non vitrial-retinal specialist and that might also lead to some sort of prolonged observation letting things progress further than they might otherwise need.

DR. FONG: This is Donald Fong, again. Dr. Ringel?

DR. RINGEL: I am not an ophthalmologist. I am a dermatologist. This question may be ophthalmologically naive but I am going to go with it anyway. I was wondering if there has been any stratification for duration of the vitreous hemorrhage. The reason I am asking is that, as I have listened to the committee, it seems that one would want to use this agent as early on as possible, perhaps at least during the first three months whereas, in the study population, most patients that had had their vitreous hemorrhage for more than three months, and it seems as if the study population is not the same as the population it is going to be used on.

I would like to know if there is any

stratification done specifically looking at safety issues.

DR. FONG: Lisa?

DR. GRILLONE: I will answer the last part of your question first, Dr. Ringel. We did not look at duration of hemorrhage as stratification for safety issues. For the first part, in terms of efficacy, because the study was not designed with a maximum limit on the duration of hemorrhage, it was not possible to stratify well the duration of hemorrhage at entry.

What I mean by that is if we look at the minimum, we have 30 days. If we look at the mean, we have about 120 days. Nevertheless, there was a fair proportion of patients who actually had a hemorrhage duration greater than 90 days and some for quite into the hundreds of days. So, given that broad spectrum in this clinical trial, it is not possible to, then, subset duration and get meaningful information from that.

DR. BULL: Jonca Bull. On this same point, the data provided by the sponsor has a duration of baseline vitreous hemorrhage with a mean, on the integrated analysis, of 120 days, about four months, for duration. I was just

wondering how does that data address the question raised by Dr. Ringel?

DR. GRILLONE: It has a mean of 120 days with a standard deviation of 110, so you could see the broad range around that. It addresses it, basically, by confirming that, with such a broad range--if there were a tighter range around that four-month period, then you would know that you can get a tight subgroup analysis.

But you really can't get a very tight subgroup analysis because the range goes from 30 days, in some patients, through beyond 120 days and beyond 230 days, based on the standard deviation, and greater. So there is such a broad range, the subset analysis would be uninterpretable.

DR. BULL: I would like to point out, this raises, I think, some significant challenges for us from a regulatory perspective because, in terms of trying to write a label, you have to base it on the data. Given that you have patients that have fairly--I guess, if you go with your mean, four months into a hemorrhage, this does not address whether or not you could articulate in a label any indication for patients, as I think someone had mentioned, who were early in the course, because

you don't have data to substantiate its use.

DR. GRILLONE: We didn't design the study to look at that small subset. Yes; we all agree on that but perhaps one of the physicians could address their feeling of how they would treat patients now based on the data that we have put before you if they had a patient with an earlier hemorrhage. What would the opportunity be for them there? Dr. Packo will address this.

DR. BULL: Excuse me. That would be speculative. I don't think it is helpful for us to go that route.

DR. GRILLONE: Okay.

DR. BULL: Thank you.

DR. FONG: This is Donald Fong, again. Let me come back to Dr. Tan about sort of the evaluation of the composite outcomes. What is your thinking on Vit-02 and Vit-03?

DR. TAN: I think the composite score outcome is not really validated. I think, then, the question is can we dissect that and extract useful information, as you cannot take the p-value given here based on the composite score entirely. If you say some of the component of it is clinically meaningful, then we should analyze that

component.

DR. FONG: I am not sure I understand that. Can you rephrase it?

DR. TAN: I think the composite, the outcome is not--I think the correlation or how this is correlated with clinical outcome hasn't been validated. That is the issue, original issue. So, in the analysis of Vit-02 and Vit-03, the Vit-02 is significant but Vit-03 is not significant. So it is really hard to conclude, make an inference out of this, for me.

DR. FONG: So we have one study, Vit-02, that shows some positive findings at Month 2 and not replicated in the third month. How do people feel about that? Dr. Wilkinson? Dr. Pulido? Dr. Feman? Members of the group?

DR. WILKINSON: As I have already said, I think that there is no way to make this an optimal statistical study with clean outcomes. I think the big picture for me is that something does happen when these eyes are injected and it is clear to me that a patient has a significant chance of having some clearing of the media as well as some iritis if they are injected. I think that that would help me manage these patients.

There are differences in each study. We can analyze these subsets until the cows come home. I am always guilty of looking at big pictures and not small pictures, but the bottom line is--and this is the reason the first question I asked was to stratify them on the basis of when the hemorrhage occurred because one of the sponsor's consultants, Dr. Packo, mentioned that, for him, the first step, if you can't see an individual's fundus and they have a big hemorrhage, the question is how active is this retinopathy. What is going on? What do I need to do? That is the patient that is going to get this injection and I think the chances of clearing are better with the injection than with no injection.

It is unfortunate that more people don't clear.

DR. FONG: This is Donald Fong again. I just wanted to clarify, make sure I understand your perspective in this. What do you base the assertion that there is clearing on, because it is not replicated in this studies.

DR. WILKINSON: It is my impression, just looking at these data, that in each and every instance, there is a 50 to 100 percent difference

at each time period on the multiplicity of the outcomes that have been looked at, not always as statistically significant with one subset as another, but it is pretty apparent to me.

Again, this is big picture, not small picture, that this drug is doing something. It is doing something important. It is not doing it optimally. I wish the number were 75 percent instead of 35 percent, but it seems to me that it is pretty clear something is happening.

DR. FONG: Pat, let me ask this question. Sometimes, it is hard to tell, when you look at 100 different sorts of looks at something, and sort of get a gut feeling for whether something is statistically significant or not, or whether it is real or not.

So, when you look at a bunch of things, sometimes it is hard to tell what is real and what is occurring just from chance. One of the purposes of statistical testing is to give you sort of a valuation of whether the findings that you are seeing is due to chance.

So, if the testing doesn't confirm it, then I am just wondering how one would sort of make the assertion that there is something happening, I

guess is what I am trying to get a feel for.

DR. WILKINSON: Well, thank you. I don't know much about statistics, but I know that that is what they are for. Again, there are subsets in which the data--Dr. Harris' nice presentation pointed out, the data do appear to clearly support the fact that something is happening.

There are other subsets in which the data are not statistically significant at a very, very high level. Again, I feel there is clear evidence here that something good is happening. These are eyes that have been loaded with blood for months. When we start talking about vision, we haven't talked about macular pathology in Type II diabetics.

This is an exceptionally complicated deal. We can fine-tune it forever, but I cannot escape my conclusion that something is happening in a disappointing minority of patients, but, still, something is happening that is not happening in the control cases.

DR. FONG: Dr. Harris, would you like to respond? Can I just follow up with one sort of observation? I think what Dr. Harris has shown is that there have been three outcomes. We looked at

it with three different doses and you looked at it at three different times. If you look at things a lot of times, you are likely to find a difference just on chance alone.

So I guess my question is how would one differentiate chance alone if you don't use statistics. I don't want to belabor the point. Maybe Dr. Tan can sort of shed some light on this.

DR. TAN: That is the point. That is why you would use statistics. That is what the whole clinical trial is all about. You don't want to base it on, obviously, a subset of patients that the drug is working. I actually agree that Vitrase is doing something very good. But it is just not so clear. In a way, you say the control group doesn't do any--in a way, I think, to me, from the--I think the control group, the saline group, is doing something. They have the same success rate, but it just came one month later.

They have exactly the same, or almost exactly the same, success rate as the Vitrase but it comes one month later.

DR. FONG: So your point is that the control group came to that same outcome one month later

DR. TAN: Right. That is consistent for the amount on the table for efficacy that has been presented.

DR. FONG: Dr. Pulido?

DR. PULIDO: I think what we are all wrestling with is the fact that it is not a penicillin. It doesn't have a 100 percent success rate. The success rate is 30 percent versus 20 percent for the control. The statistical significance, especially after taking Bonferroni calculations, or whatever, becomes very, very questionable and very marginal.

But it still appears every time to show a little bit of effect. Again, I harken back to--I am concerned about the Feman factor which is the use of this by people that are not knowledgeable, by non-retinal specialists. Maybe in the labeling, we can make sure that there are some instructions on when to use it.

But, for us that see these patients that are on Coumadin or have tremendous medical problems that can't be taken to surgery, it gives us at least a chance to maybe help these people.

DR. FONG: Dr. Brown?

DR. BROWN: I just want to add that. If

you look at the different ways, and you sort of put the question to us as to say finding out at two months versus three months, when is that really going to help you clinically. There are certain situations where we know, from the diabetic retinopathy study, old data, but, in certain situations, we certainly know that earlier treatment is better, in certain clinical situations.

The second issue is the functional standpoint and just how does this patient get along in their own life. If we can increase it from being two out of ten to maybe three or three-and-a-half out of ten who can actually get back to functioning, well, that is a good thing.

Then the next part of it is at what risk am I putting the others in that group of ten to get that one or two? From my view, the iritis and hypopyon seem to be easily managed without significant sequelae, no increased risk of neovascular glaucoma and these issues. The one thing that I was interested about was the retinal-detachment rate which appears to be higher. Whether or not we actually are inducing traction or is it that we are seeing it earlier. I don't think

we know the answer to that.

But, on the whole, I think that, to get that added benefit for those extra people in that group of ten, I think that the risks are reasonable.

DR. FONG: The sponsor?

DR. CRAIG: I am Dr. Craig. I am in charge of preclinical work. I wanted to address the Feman factor if I could, for just a second. Dr. Feman, you had a concern you stated about retinal damage. I didn't have a chance to jump up and talk about a primate study that we have done. You were addressing it specifically, I think, for where the vitreous had been removed and then the product injected.

We haven't done that but we have injected the product into primate eyes without hemorrhage, twelve animals per arm and doses, in one arm, two to three times higher than the 55 IU dose and the other was four to six times higher. While we did see iritis, it did resolve itself as it has in the patients in the clinical trial.

There were some effects on the retina due to the inflammation but there were no permanent toxicological effects on the retina.

DR. FONG: Just to be the devil's advocate here, Dr. Brown--this is Donald Fong--I think there are two issues that this drug might be useful for. One is potential visual benefit to the patient leading to improvement in visual function and the other is improvement in the ability to diagnose.

I am just sort of thinking aloud. I would like to hear what the other members think. It is hard for me to ascribe a benefit that doesn't last. So I am just going to that point first. One could argue that there really isn't a visual benefit because it doesn't last. I want to throw it out and see what people think about that.

DR. WILKINSON: Don, with all due respect, I--

DR. FONG: Dr. Wilkinson?

DR. WILKINSON: Yes; Pat Wilkinson, once again forgetting to state his name. I wouldn't expect this necessarily to improve vision. That is certainly not a realistic endpoint. These patients have vitreoretinal pathology. They all need--the vast majority need some kind of treatment. Unless you spontaneously avulsed the vitreoretinal adhesion with some movement of the vitreous gel, you still have a traction upon abnormal blood

vessels.

There is no way that you can expect chronic permanent improvement in vision. This is, to my way of thinking, simply a management tool to allow you to differentiate a person who needs Treatment A from Treatment B from perhaps occasional observation.

But it is a treatment tool and certainly not a cure or a means of improving vision directly. It is a means of improving vision indirectly by eliminating blindness.

DR. FONG: I guess my question is, to follow up on that, is it a helpful tool. If the patients need a vitrectomy anyway, what have you gained by doing this injection. Now, this injection is not horrible. The risk of ophthalmitis, risk of retinal detachment is not huge, but it does cause a lot of pain.

60, 70 percent of the patients complained of pain, even with the saline injection. So this is something that patients may not tolerate. Now, we don't really have data on that right now. A lot of patients withdrew. 10 percent withdrew. So it is not completely a harmless diagnostic tool. It is an invasive procedure and if it is only allowing

you to diagnose something one month earlier, is that helpful?

DR. WILKINSON: Pat Wilkinson. I think it is exceptionally helpful. The one month is critical. But let me go back to my original statement. The critical issue here is being able to figure out where you are. We know from all of the ETDRS, DRVS and DRS trials that certain people don't necessarily need more laser or a vitrectomy. They can even be allowed to, again, become blind from the hemorrhage, assuming their other eye is okay. But there are others with very, very active, relatively new retinopathy that we know will progress like crazy, and certainly over a month.

These people can be identified and then managed appropriately. So I think a transient peak is exceptionally valuable and probably the main reason to give this injection. I don't want to sound condescending but I think we all, sooner or later, need to ask ourselves a question, what if I had a proliferative diabetic retinopathy and I wasn't even at high risk but I had a massive hemorrhage. Maybe I was pagged for a couple of days. I'm not clearing at all. Would I want this drug injected? I can assure you that, based on

these data, they are not sensational but I am impressed that I would want the injection.

DR. FONG: Comments? Dr. Pulido?

DR. PULIDO: I am not sure that, necessarily, I would, especially being an Hispanic. The data is still questionable as far as I am concerned with that. But I think, again, going back to the group that I envision this was used in, if 25 percent die within the first year, and you give them one more month of vision, it is back to the time of the AIDS patients with CMV retinitis where we could keep their vision for a month, two months, three months with gancyclovir. Their quality of life might be a little bit better. So, because of that, I think it is reasonable.

DR. FONG: Paula?

MS. KNUDSON: I would like to ask a question. Diabetic patients would be at risk for the vitreous hemorrhage all the time. So you have had one in one eye. You have now taken care of that. You have had the injection and then the vitrectomy. What happens if the other eye becomes affected. Is this drug something that you could use again in the other eye? There is no contraindication to using it twice?

DR. WILKINSON: No, but let me clarify. Pat Wilkinson. The major problem in dealing with this epidemic in our country is getting these individuals into the office. Someone shows up with a vitreous hemorrhage in one eye and they receive this injection. We hope they won't need a vitrectomy. We hope they will need laser and that is why this surrogate analysis was reasonable, although not clean.

Once they are in the office, then we know, through these previous collaborative trials, who is at risk and so we hopefully can treat them appropriately long before they would even have any risk whatsoever of a hemorrhage.

DR. FONG: Dr. Tan and then Dr. Pulido and Dr. Steidl.

DR. TAN: I just want to--I think Dr. Wilkinson said you would actually expect to see improvement of vision, but the study, the trial, was actually to show exactly that. So if that argument stands, I am having a very difficult time to interpret the data.

DR. FONG: Can you elaborate what you are saying?

DR. TAN: I think if Vitrase is really

expected to just enhance your diagnosis, or make a better diagnosis instead of increasing the acuity, as the sponsor has presented it, the most study should be just on how to increase the diagnosis, the utility of this drug.

DR. FONG: Can you summarize for me?

DR. TAN: I think the study was designed to show improvement, you know, acuity; right?

DR. FONG: Yes.

DR. TAN: So now what I am hearing is we are not expecting this drug to show any improvement of acuity here. So what do we expect this drug to do, then? We are back to the earlier question what benefit does Vitrase bring to the patient. It is not clearly defined to me.

DR. FONG: I think what Dr. Wilkinson has said is that what this drug allows the clinician to do is a temporary look at the retina and the pathology and the disease in the retina and then this will help guide as treatment. The question is--there are two questions. From your standpoint, I guess, Dr. Tan, maybe is does the data support that.

DR. TAN: Therefore, it is how successful this will guide you. That would be the information

we want.

DR. FONG: Let me go down the list. It was Dr. Tan, Dr. Pulido. Dr. Pulido?

DR. PULIDO: I think Ms. Knudson's was actually an excellent question. At first thought, you would say, well, treating the second eye shouldn't have any effect. But, on the other hand, this is an inflammatogenic protein and it is a foreign protein. So the question is whether you inject in the second eye, you would increase the amount of inflammation. We don't know the answer to that. I think it is an excellent question.

DR. FONG: Dr. Steidl?

DR. STEIDL: This is Scott Steidl. I think we all would love to have this thing work and be efficacious and be something that we could offer patients. Perhaps each of us would choose to have it done in our own eye. Just from the data, and I am not a statistician, it is not quite clear to me what it is saying.

I think that these are very complicated, though. Some patients you suspect, wow, I really missed giving that laser treatment and now I can't see. Then there are other ones, you look at the fellow eye or you know the history and you really

suspect maybe there is a little patch of peripheral neovascularization and it bled, but they can probably be followed.

So I think it is kind of hard to generalize. So it seems to me that we are saying that the people that might benefit early, and it may be a different group. Maybe it is not a group of medical necessity but people who just need quicker visual resolution. They may benefit, but the problem is that it affects a small percentage.

So if I am getting a consent, I would be saying, maybe 10 percent chance, but you could have eye pain, retinal detachment, inflammation. One thing maybe someone could address, some of the physicians that have used this, but, from my point of view, hypopyon is infectious until proven otherwise. I am nursing someone with a sterile hypopyon right at the moment. My blood pressure went up a bit when I saw it. I bit the bullet and I didn't inject.

But I think that this is not to be minimized. I think that, in a lot of the literature, it is described as, oh; it is just a hypopyon and we will manage it. I would be curious to see what people might say about your

constitution, seeing that many patients with it.

DR. KUPPERMAN: To address the two parts of that question, first the issue of eye pain that has been raised a couple of times. Eye pain was recorded in the context of a clinical trial but, having injected this many times, it is the standard eye pain that is present from--if you were to ask any patient after any intravitreal injection, whether that was gancyclovir or foscarnate in AIDS patients, triamcinolone in the other patients, et cetera.

So this is not an exaggerated response, sir, to an intravitreal injection. It is the standard when you ask a patient--we don't ever bother asking them outside of the clinical trial do they have pain. So it is a small amount of pain. I want to put it in that context.

In terms of the hypopyon issue or the inflammation issue and how you react to that compared to an endophthalmitis or how do you stop yourself from reacting to it, because we are all trained to think about a hypopyon the day or two after you give an injection as endophthalmitis until proven otherwise.

Two issues. One is that it doesn't look

like the classic endophthalmitis. It is not a hot, inflamed eye. It is not massive injections. It is not that extraordinary pain. It doesn't have the other clinical features that go along with endophthalmitis.

Secondly, by our experience, again, not one case out of all the 1500 patients that have been injected have we seen even one case of injection-related endophthalmitis. There was, I think, one case that was two months after a vitrectomy, six months after an injection, something like that.

DR. STEIDL: Are you approaching these patients differently than one that you suspect is infectious?

DR. KUPPERMAN: Yes.

DR. STEIDL: Fewer visits and that sort of thing?

DR. KUPPERMAN: Oh, yes, because it is a consequence injection, we think that--again, we know that there is iritis. Again, my patient population, Jose, to address some of your concerns, again, in the limited population has been largely Hispanic and I have not seen any untoward severity of inflammation in terms of manageable amounts of

iritis after this injection. I am sensitive to that patient population, being a family from Brazil, as well, my own family, and have been sensitive to that. I have not seen an untoward amount of inflammation in those eyes.

So, again, it is a retraining of your mind set because one does want to react to that as if it is an endophthalmitis but, given this known inflammatory consequence, it is a retraining that will need to be done.

DR. STEIDL: I guess, just quickly, the corollary of that is if we downplay that, who knows. Maybe Vitrase is protective against endophthalmitis. I don't know. But if we take a more cavalier approach to it--it is kind of hard to say that you can put down your guard. I don't know. Then you might--

DR. KUPPERMAN: I continue to have an index of suspicion but, again, without that beefy looking conj and some of the other factors that go along with it, there tends to be just redness at the injection site, a quiet otherwise looking conjunctiva and episcleral vessels, et cetera, and inflammation inside the eye and/or a layered hypopyon. It is a different picture than one would

normally be concerned about with a classic endophthalmitis.

DR. FONG: The sponsor?

DR. CRAIG: Bill Craig, again. I wanted to address Ms. Knudson's question and the response to it. It is along the same lines. In that monkey study that I mentioned, we did have an arm that received a second injection of the product. As I mentioned, the first injection caused the type of iritis that we expected to see. Once that had resolved to a great degree, we did a second injection. We saw almost exactly the same reaction. It was certainly no worse.

In fact, I was just looking over the data the other night. The hypopyon was reported in the first injection but, interestingly, there was no report of hypothesis in the second injection and it resolved as quickly as it did on the first injection.

DR. FONG: Dr. Feman?

DR. FEMAN: I am Steve Feman. I would like to expand on what I think Dr. Tan was trying to get at earlier and correct me, Dr. Tan, if I have misinterpreted what you have said. The impression is that, if the drug does not improve

visual acuity which is what we all seem to be talking about. But its major effect is that it works to allow the physician to see the retina better. Is there any data in the packet that we have received that proves that? Is the data designed to show that? Is any part of the study designed to show that it allows the physician to see the retina better?

It may be here and it is just that I may not have seen it.

DR. TAN: I don't see it either.

DR. FONG: Dr. Wilkinson? Do you have any follow up, any thoughts on what Dr. Feman said?

DR. WILKINSON: Pat Wilkinson. I don't have any thoughts but I can reiterate what I have said. I think the surrogate analysis, the fact that--I was just trying to grab Dr. Harris' data to see if I could find anything there. Perhaps you would be the best person to answer, Dr. Harris.

It just seems to me that there was 50 to 100 percent greater chance that the patients could be managed in some fashion if they receive the drug.

DR. FONG: Dr. Harris?

DR. HARRIS: I think you are asking about

the proposed composite, that endpoint that says, can we see it and, from a physician's standpoint, are they able to see it and treat patients better. We need to look at both trials independently because we need validation from both trials in order to make a decision.

We can't base all of our experience on one trial. That could just happen by chance. So we look to see if it has been replicated. That is why I presented these two charts. We looked at Vit-02 to see what it actually showed. I agree that, in Vit-02, it shows that there does seem to be some efficacy for the 55 units of Vitrase in the first two months.

But when we look at the Vit-03 trial to see if anything replicates, it is a failed study. It doesn't show that anything replicates. So we base our decision on which trial? Do we base it on Vit-02 and say that we see something or do we base it on Vit-03 and say that there is nothing?

DR. FONG: Dr. Phillips?

DR. PHILLIPS: Bill Phillips. I just had sort of a general comment, too, from the actual practice standpoint. Initially, in their NDA, they were stating that vitreous hemorrhages are

typically observed for six months. That was true in the past. Then some of the physicians that were speaking on behalf of the sponsors would say, well, we will typically watch a vitreous hemorrhage for three months.

That is certainly possible and could fall within standard of care. Standard of care certainly varies from region to region. In the Washington, D.C. area, when you are looking at the majority of the patients that were enrolled in this study, all being 20/200 and worse and most either count fingers, hand motion or light perception, they would not end up waiting three months for a vitrectomy.

So, if we are looking at the efficacy in the 55 International Unit group being at two months, we are getting a view. Very few of the patients in this area even would wait two months with that dense of a hemorrhage. So that is one thing. We are sort of comparing it. I understand, within the context of the study, we have to compare it either to watchful observation or saline.

But there is also another alternative which is the vitrectomy that, in the real world, has to be discussed with any patients except for

those that medically could not undergo a vitrectomy which may end up being the best indication for this drug. I think it would be very useful then.

The other thing is just looking at the endpoint in the composite of it is clear enough that we can now see the retina to make a determination of treatment. If that treatment is just laser and it stays clear long enough that we can do that, that's great. But the data also shows that, in many cases, that determination was there is a retinal detachment which ended up needing the vitrectomy anyway. So you have now gone through two procedures, the injection and then the subsequent surgery.

I think we have to take all those points into account in looking at the efficacy overall.

DR. FONG: Dr. Feman?

DR. FEMAN: I just wanted to speak to what Dr. Phillips had been addressing. The reason why the three-month, four-month interval has come to practice is that, in the original derivation of the diabetic retinopathy vitrectomy study, it was found that at approximately four months, you can start measuring electroretinographic abnormalities by doing bright-flash ERGs, that there was a retinal

toxicity from the iron in the hemoglobin being present in the eye so long.

That is why the time intervals have gone from six months down to three to four months. But I think that is where the standard is now. I don't think there are very many practitioners anywhere in the United States that would wait more than three months before doing a vitrectomy because of the danger of having retinal toxicity, of having the blood in the eye that long, which leads us back to this study that we are examining right now, when many of the eyes that were enrolled in the study had the blood present for 121 days, as I recall from an earlier slide.

Correct me if I am wrong, but I thought that they said that the average entrance patient, the mean of the entrance patients, had blood in their eye for 121 days which is longer than the standard in most parts of the United States.

DR. FONG: So what is the corollary? Is there a corollary to that, Dr. Feman?

DR. FEMAN: Again, I just see the value of this medication other than as a chance of delaying a vitrectomy that the patient might need. Again, I have this great concern about toxicity, not

necessarily from the drug, perhaps, but from the blood having been present in the eye so long.

DR. FONG: At some point, we will need to take a vote on the questions. But it sounds like there is some more discussion. Dr. Wilkinson?

DR. WILKINSON: I wanted to speak even though I don't disagree--Pat Wilkinson, by the way--with Dr. Feman's premise that, in fact, those of us that are old enough to have been around when vitreous surgery began, our best cases, we operated on even before the lie-pipe was invented, had had an eye full of blood for twenty years. This toxicity may be visible on an ERG but many of these patients did beautifully.

If their macula worked well, they had an absolutely phenomenal outcome. So I don't think blood toxicity is a critical issue. I would agree with Dr. Phillips. I think very few people will allow observation for three months.

But, again, if the patient--the critical thing is the activity of that retinopathy. If the patient has had scatter, this is something Emily wanted to get into, how many eyes had already had scatter. If a patient has had scatter, they are at no risk for tremendous proliferation and they are

into just some mild traction, they can be watched indefinitely if their other eye is okay.

If they have very, very active retinopathy that has never been treated, then they critically need treatment immediately. So the concept of a preoperative management tool is, to me, the most appealing.

DR. FONG: Dr. Chew?

DR. CHEW: I just have a comment, I think, more than anything else. As a clinical trialist, there are a lot of shortcomings of the study. There is no question. I think we are having trouble trying to decide one way or the other. We don't have a good endpoint. There isn't a good endpoint here. It is a difficult situation. These are tough patients.

As a clinical trialist, I don't like the trial because I think there are many things that we would have liked more information on. But it is what it is. The patients, themselves--I think we are going to come down to deciding as clinicians more than as biostatisticians or clinicians who do clinical trials because we don't have that information in front of us that really allows us to make that information really in an informed way.

I think a lot of it is going to boil down to what would you do as a clinician and how would you feel as a patient if you were in the situation. Then it becomes a balance of how much harm are you doing to these patients. How bad is this hypopyon?

If you look at it, 55 IU, I think hypopyon was, in the first trial--was it about 1 percent? Is that right? So it is not like it is an outrageous amount. We are not talking about a huge amount of complication. So I think a lot of this has to be really balanced on how we are going to--we are looking for Dr. Tan and others to give us guidance. I think that is why FDA has us here because, if they knew they had a good statistical method, they would have it approved by now. They would have it approved and all finished.

So I think a lot of it has to be discussed, the balance of the two, in terms of our practice.

DR. FONG: Dr. Dunbar?

DR. DUNBAR: An issue I would like to bring up is that this is a novel therapy and the decisions about this therapy will serve as a precedent for other therapies in the future. Because the clinical situation is so grave for

these patients, it is very tempting to us to lower the bar. However, we may be lowering the bar for many years to come and thus discourage even better therapies that may be just around the corner.

DR. FONG: Dr. Steidl?

DR. STEIDL: Just a quick question for the company. Was there quality-of-life data obtained?

DR. GRILLONE: No; there was not. It was not designed to look at quality of life.

DR. FONG: Dr. Tan?

DR. TAN: I just want to put the assessment of adverse events into the perspective. Of course, the trial wasn't designed to show any difference in terms of toxicity. Of course, not. For the original--it is 4.2 versus 6.9. Those are not significant. The difference is something we should focus on. There is about a 3 percent difference. Of course, they are not going to be significant.

Most of the time, they won't be significant because that would require a lot of patients to show a significant result. That would be after the drug is approved and in the postmarketing scenario. They will see more patients. Then you become significant.

So I just want to put this assessment of the adverse event into perspective. The magnitude is what we should look at.

DR. FONG: Why don't we take a look at the questions. Are there any objections to looking at the questions?

Questions and Vote

DR. FONG: What I would like to do is I would like to read the question and go around to each of you and have you comment on the answer, or answer the question.

Kimberly just told me that we need to look at the questions that are attached to the agenda, not the book, the page following the agenda.

The first question is--maybe we will just start on one side of the room. I don't want to start with the statistician. Maybe we will start this way. Well, we will start with the statistician.

The first question is has sufficient evidence been submitted to support the efficacy of Vitrase for the treatment of vitreous hemorrhage. Dr. Tan?

DR. TAN: No; I don't think so. It is a yes or no question, so I will just say no.

DR. FONG: Any comments to follow that?

DR. TAN: First of all, the efficacy--there is a conflict in the result in one trial--there are two major pivotal trials. One is significant and the other one is not. Also, in terms of what is efficacy. Efficacy is not really well-defined.

DR. FONG: Thank you, Dr. Tan.

Dr. Phillips?

DR. PHILLIPS: Bill Phillips. I would also say no. The three-month data lost the visual benefit, I believe, for the 55 International Units. Even just as far as the treatment outcomes, I would need to see that stratified more to really be sure that that was providing a treatment benefit over the watchful waiting of the saline group.

DR. FONG: Dr. Chew?

DR. CHEW: Emily Chew. Given the endpoints that were stated, I don't think we have that evidence for efficacy. One thing I would like to see, it is sort of on the next question, what additional studies are needed to establish, it would be nice if I were able to see the data that looked from--

DR. FONG: We will come to number two in a

second. Let's just do number one.

DR. CHEW: Okay.

DR. FONG: Do you have any follow up to number one?

DR. CHEW: No. I think it is the issue of the endpoint which we can't really have a good handle on in this particular study. I think, for me, vision would be a very important aspect of this given the composite was more difficult, although I know it is a different clinical question we are asking there.

DR. FONG: Dr. Wilkinson?

DR. WILKINSON: Pat Wilkinson. I would vote yes. The endpoints are not optimal. The study is not optimal. The data are not optimal, but there is a very, very clear trend in most of the subgroup analyses that there is a genuine change in the vitreous gel following the injection. Let me also comment, I don't disagree with Dr. Dunbar, but I think we can all learn from studies. We can all insist on better studies next time, but to state that we are lowering the bar by considering acceptance of this application seems to me to not necessarily be the question.

DR. FONG: Dr. Pulido?

DR. PULIDO: Jose Pulido. I would say it is minimally effective and there does appear to be a slight improvement in vision, improvement in peripheral visualization. I guess, with respect to what Dr. Dunbar said, I would hope that the next drug would have a better effect overall.

DR. FONG: Is that an acceptable answer to FDA? No? We want a yes or a no.

DR. PULIDO: Minimally, yes.

DR. FONG: Dr. Brown?

DR. BROWN: Jeremiah Brown. I would say, in the application to improve visual acuity at two months that, yes, it was shown in both Vit-02 and 03 a statistically significant benefit. And then, in terms of resolution of vitreous-hemorrhage density, in both Vit-02 and Vit-03, showing a statistically significant benefit at two months. So, in that limited application, that is the benefit that I see. That is the efficacy.

DR. FONG: What is your answer?

DR. BROWN: Yes.

DR. FONG: Dr. Gates?

DR. GATES: I am certainly torn between both camps here. I believe that efficacy in the population as a whole, and scientifically, wearing

my scientific hat, I would say no. Taking care of the individual, I think there are individual patients out there that would certainly benefit. But I think I have to vote, as far as for the population as a whole, and say no. The data doesn't show.

DR. FONG: Donald Fong. I wanted to commend the sponsor on tackling a tremendously difficult problem, being the first in the field to investigate the treatment for vitreous hemorrhage, tremendously difficult endpoints that are hard to come by. I think it is a very important area to study.

However, I am concerned about the surrogate endpoint. What I am concerned about is the connection between the endpoint and what we are ultimately interested in which is vision. I don't see that connection being presented and being supported. So I have concerns about the endpoint and I also have concerns about replicability.

It seems like each study shows positive findings in different endpoints. So that suggests to me that chance might be playing a role here. So I would answer no.

Dr. Feman?

DR. FEMAN: I vote no, also. I believe that the problem is that the endpoints that we are looking at are not endpoints that were accepted by the FDA as was initially proposed. Therefore, if we are looking at just the evidence that was submitted in terms of what we are expecting to see, the answer is no.

DR. FONG: Dr. Dunbar?

DR. DUNBAR: I also vote no. I share Dr. Brown's observations that, at two months, visual acuity and density of hemorrhage did show statistical significance and it was replicated between both trials. But, again, as others have observed, there were so many endpoints. These were not the primary endpoints as the study was initially designed.

DR. FONG: Dr. Steidl?

DR. STEIDL: I guess the way the question is worded, I would vote no, too, given my concerns about the surrogate endpoint, like Dr. Fong's. The marginal benefit of three-line vision and hemorrhage at two and then not being carried through to three months, and then it not being shown with the primary endpoint.

MS. KNUDSON: Paula Knudson. I am

persuaded to say yes on the basis that if it does provide some patients with earlier and better management, I think it is worth having.

DR. FONG: I would like to move on to Question No. 2, if there are no objections. Kimberly wanted me to report the vote, which I have, which is four for yes and eight for no to Question No. 1.

Question No. 2 is, "If not, then what additional studies are needed to establish the efficacy of this product?" To answer this very basic question, I am going to start with Paula.

MS. KNUDSON: I am insufficiently well versed to know what kind of studies should be designed.

DR. FONG: Dr. Steidl?

DR. STEIDL: In addition to a lot of things I would like to know including how it might just stack up to vitrectomy surgery. I think the one thing that I would like to know more about is just plain quality of life. In reading this, as was clarified, the pain might not be what it seems when you are reading this. A lot of these things might shake out a little bit differently if you were really asking patients detailed questions

about what their experiment was and the value of it.

DR. FONG: Is that enough clarification for you? Okay.

Dr. Dunbar?

DR. DUNBAR: I would be interested to know if there is some subgroup of these patients, if all the of the diabetics were sorted out, if patients with earlier hemorrhages were sorted out in these kinds of situations, if there is a subgroup this is especially useful for, perhaps even just redesigning the study based on the information here, the density reduction at two months and the visual acuity improvement at two months, may be enough to help the company to achieve approval.

DR. FONG: Dr. Feman?

DR. FEMAN: I am sort of surprised that the company did not pursue the surrogate endpoints to an acceptable level for FDA approval. Somewhere in the packet that we received, they had initially suggested some surrogate endpoints and then it was not completed. I think that is what needed to be done is to prove that the surrogate endpoints that seem to have some value to them are still worthwhile. I think they need to look at these

surrogate endpoints and make them an acceptable endpoint.

DR. FONG: Donald Fong. I go back to what I have said earlier. When I do anything to patients, I want to know that I am doing something that is helpful to them. What I like to see is evidence to support that this actually is doing something.

I think I would like to see that they are getting some useful vision back or that it is preventing a vitrectomy and, if they are getting vision back, that it is persistent. So I would like to see sort of an analysis of useful vision, vitrectomy rates and maybe the time involved, a Kaplan-Meier analysis.

I agree with what Dr. Steidl said and that is that too often--I often do this myself--forget the patient's perspective. I would really like to see how the patient feels about this, whether their quality of life improves, where they are able to recognize people better, they are more able to ambulate better, something along those lines to support its use.

Dr. Gates?

DR. GATES: I would also concur and like

to see some data with quality of life.

DR. FONG: Dr. Brown?

DR. BROWN: Jeremiah Brown. I would also like to see quality-of-life data and also validation of the surrogate endpoints. I think that these are very useful. If we could show that earlier treatment, earlier visualization actually made a difference in the outcome for the patient, then that would make me feel even more positive about it.

DR. FONG: Dr. Pulido?

DR. PULIDO: I had voted yes, so, because of that, I will forego answering Question No. 2.

DR. FONG: Dr. Wilkinson?

DR. WILKINSON: Pat Wilkinson. I would like to defer my response to Question 3 except to point out that I think these endpoints were poorly stated. To look at this drug as a drug to improve vision, or to improve quality of life just because it is stuck in there, is not particularly relevant. I don't think that, theoretically, you really would expect that without some kind of additional therapy in most cases.

DR. FONG: Dr. Chew

DR. CHEW: I don't have much more to add,

other than the quality of life. I think it is very important from the patient's point of view.

DR. FONG: Dr. Phillips?

DR. PHILLIPS: I had coming at the end of the line. I have to echo everything everyone said about the quality of life, since Vitrase is not really designed to treat the underlying condition but just treat the vitreous hemorrhage. So we need to know how much is that treatment improving their quality of life versus a gold standard for treating vitreous hemorrhage such as a vitrectomy.

DR. FONG: Dr. Tan?

DR. TAN: I would like the company to revisit what are the really expected benefits for this product. If the product is really based on the mechanism or the size, the product really leads physicians to better diagnosis, then build the endpoint on that.

DR. FONG: Any more observations about Question 2? Dr. Wilkinson?

DR. WILKINSON: Pat Wilkinson. Don, I would like to make one additional comment regarding quality of life. It is critical. We all believe in it, but Paul Lee, of Duke, has done extensive analyses and interviews with patients. There are

certainly many patients that have been optimally treated with heavy scatter photocoagulation who have had blindness prevented--no doubt about it--who are exceptionally unhappy. So I would recommend that they are very careful on how they structure these quality-of-life interviews because not every patient appreciates all you have done for them as opposed to to them, Don--that you have done for them.

DR. FONG: As a retina specialist, I echo that. Let's move on to Question No. 3. "Are additional analyses of the current data needed to understand the efficacy or safety of Vitrase for the treatment of vitreous hemorrhage?"

Dr. Tan, would you mind if I started with you, again?

DR. TAN: Okay. If they can get some--I don't know if those data are available. It seems, for the final outcome, whether they would need a better outcome from the patients with vitrectomy due to maybe an earlier diagnosis of the possible clearing of the blood. So this type analysis, a time-to-event analysis, would be useful.

DR. FONG: Dr. Phillips?

DR. PHILLIPS: I guess one thing we were

looking for, or looking at, would be if there was maybe a little bit better visual-acuity qualification early on, sort of admitting we can't do a logMAR for the 28,000, as he indicates, maximum number of patients. I would like to see that, but I think that would be very difficult.

DR. FONG: Actually, I was reminded that Question No. 3 is a yes/no answer. So I have to go back to Dr. Tan and ask him, are additional analyses of the current data needed to understand the efficacy or safety of Vitrase for the treatment of vitreous hemorrhage? Yes or no?

DR. TAN: That would be yes.

DR. FONG: Dr. Phillips?

DR. PHILLIPS: I will vote yes.

DR. FONG: Dr. Chew?

DR. CHEW: I would say yes. I would like to go down the same line that Bill Phillips is going down. I would like to see analyses looking at that very severe n and, instead of giving them one line for each jump is to consider them all to be at zero and see what happens, what proportion would actually gain fifteen letters if we start off with that. I can't tell from the data here, although, at one month and two months and three

months, and see whether there is some improvement from that.

DR. FONG: Dr. Wilkinson?

DR. WILKINSON: Pat Wilkinson. I initially responded yes, so I am responding yes again, as illogical as that may sound. I kind of agree with what Dr. Dunbar brought up and that is, if you can, perhaps, restratify these cases and particularly look at the relatively fresh hemorrhages and somehow identify what the doctor was able to do for that patient, or to not do, and comparing the control and the treatment arms.

DR. FONG: Dr. Pulido?

DR. PULIDO: Jose Pulido. Yes, there are other data that would be worthwhile looking at. The Bull-Dunbar effect, stratifying in terms of how long the hemorrhage has been there, determining whether there are differences and number of patients on Coumadin in one group versus Coumadin in the other group. Mentioned time and again, are differences in race and it might be worthwhile, if there are any second eyes that have been treated, to see if there is any inflammatogenic effect in the second eyes.

DR. FONG: Dr. Brown?

DR. BROWN: I would also say yes. The visual-acuity issue is probably the most important one from what I saw. I was looking at some data that I had during the break. Jerry Fishman, who does a lot of work on patients with low vision due to hereditary retinal diseases, has a scale that he has used for assessing LOGmar in patients who cannot read 20/400, even down to count fingers.

I just noticed that the numbers that he chooses are not as beneficial--well, they are quite a bit lower than what was used for this study. So 1.84, I think it was, count fingers, he uses a much lower number at 2, or a greater number; poorer vision, in other words.

So, looking at the assessment of the LOGmar and if that were changed how that would affect the results. That is another thing that I would like to look at. Then the third was the stratifying based on the time of the vitreous hemorrhage.

DR. FONG: Dr. Gates?

DR. GATES: I would also like to see that stratification and I would say yes.

DR. FONG: I would answer yes, also. What I really want to do is really understand what is

happening. I agree with Jose and Jeremiah and Pat, what they said, that something is happening here. I really want to figure out what is happening, these patients that we are getting some transient clearing. What is being done? Does that actually lead to a treatment that affects the final visual acuity.

So I need more sort of connection between final visual acuity and the proposed outcome. Also, I agree with Dr. Dunbar that it would be helpful to know whether this treatment might be effective in certain groups.

Dr. Feman?

DR. FEMAN: I agree with you all. I agree, yes, that additional analyses of the current data are needed to understand the efficacy of Vitrase. A lot of the data is currently available, it seems, and we just have not looked at it. But I think we also need more data, but to answer the specific question, yes.

DR. FONG: Dr. Dunbar?

DR. DUNBAR: A minor point, in addition to the stratification, that I touched upon earlier. I would be interested to see a subgroup analysis of patients with previously diagnosed glaucoma for

safety issues.

DR. FONG: Dr. Steidl?

DR. STEIDL: I guess yes, in answer to the question, simply because I think further analysis might convince someone such as myself to change their opinion about the efficacy. But I agree about the early versus late treatment. That would be very interesting and of value in terms of functional vision.

Another thing I am sort of curious about is maybe a little bit more detail than just three steps, who had it, who didn't, for those who had improvement, what percentage in the treated group had five steps, six steps, seven steps, versus the control. It might be interesting to know that, if you did get an effect, the effect in the treated group would be bigger. It would be curious.

DR. FONG: Paula?

MS. KNUDSON: Yes. I would like to see the data mined for who are these patients who actually had the benefit. Is there a difference in age? Is there a difference in race? I would just like to know more about those people and see whether we could do something along those lines, maybe structure the drug specifically for a type of

patient, specific type of patient.

DR. FONG: There is unanimity that there needs to be additional analysis. That is the answer to Question No. 3. Let's go ahead and move on to Question No. 4, if there are no objections. "Should the potential interaction, positive or negative, of Vitrase with current treatments for Vitrase hemorrhage be evaluated?"

I know it is unfair, but Ms. Knudson?

MS. KNUDSON: Of course, I would have to say yes. I think it would be extremely important to know.

DR. FONG: Dr. Steidl?

DR. STEIDL: I agree yes, but it is hard for me to formulate a response at this time. If it were possible to just take equal groups and compare them to vitrectomy, it would be interesting for me. But I am not sure that that is appropriate. I am not sure what the right study is, but I think it would be--if it could be properly thought out, the answer is yes.

DR. FONG: Dr. Dunbar?

DR. DUNBAR: Actually, no. I think that the company described in various different ways the relationship between vitrectomy and the drug.

DR. FONG: Dr. Feman?

DR. FEMAN: I would vote yes. I think that the drug might be very effective in preplanning doing a vitrectomy. In other words, if what we are seeing is the correct interpretation, and I am not sure if that is, this would clear up the eye in such a manner that one could, perhaps, plan a vitrectomy although one does that when you are doing a vitrectomy. So I don't know how the drug would offer any benefit. But I still would vote yes from that perspective.

DR. FONG: I will answer yes. I think that the interaction between vitrectomy and use of this product needs to be investigated further. This is sort of what I said earlier, that it is hard for me to tell what Vitrase is doing if we are going to do a vitrectomy very soon after diagnosis anyway.

Dr. Gates?

DR. GATES: I would also say yes.

DR. FONG: Dr. Brown?

DR. BROWN: Jeremiah Brown. Yes.

DR. FONG: Dr. Pulido?

DR. PULIDO: I would say yes, only for negative, would it--just looking at the present

data and not having to do another study for the company, does the use of Vitrase in any way cause a deleterious effect following vitrectomy to vision? I don't think any further study has to be done just looking at the present data.

DR. FONG: Dr. Wilkinson?

DR. WILKINSON: Pat Wilkinson. I would agree with what Dr. Pulido just said. There really is no other treatment for this and the only question might be how it alters the performance of a vitrectomy. A vitrectomy is simply designed to create a liquid-filled cavity also eliminating the cortical vitreous. This drug does the first half of that. Since there is no other treatment but vitrectomy, what Jose said is something I agree with.

DR. FONG: Dr. Chew

DR. CHEW: I would agree with that also.

DR. FONG: Dr. Phillips?

DR. PHILLIPS: I would also say no. They essentially already have that data in that if the Vitrase works and your view is clear enough to either see, nothing needs to be done, they need or laser or a combination of laser and vitrectomy. You are already going on to those endpoints so I

don't think anything additional needs to be done for that. So the answer is no.

DR. FONG: Dr. Tan?

DR. TAN: My answer is that I agree exactly with Dr. Pulido, they don't need a concurrent comparative study because they don't really know the endpoint should be there. I think, in addition, what would be interesting or useful for us is some type of maybe a historical comparison versus a concurrent study.

DR. FONG: That is a yes or a no?

DR. TAN: Technically, a yes.

DR. FONG: Let me go back to Dr. Phillips. I think we didn't write it down. Was yours a yes or a no?

DR. PHILLIPS: No.

DR. BROWN: May I amplify just to give a reason? The one thing that I noticed in the data was that trend toward fewer vitrectomies in the Vitrase group. It would be very interesting to know what were the indications for those vitrectomies. If this is going to be a real thing, that perhaps we reduce the need for vitrectomy by 5 percent, why is that and just to see what were the indications.

DR. FONG: So the tally for the answer to Question 4 is two no, ten yes. So, if there are no objections, I would like to proceed to Question No. 5.

DR. CHAMBERS: Dr. Fong?

DR. FONG: Yes? Dr. Chambers?

DR. CHAMBERS: I would come back a little bit to the question we just asked and ask whether there is a feeling within the committee that something like the following scenario, which I want to propose, would be useful looking at. It has been discussed that there is a possibility that Vitrase would more liquify the vitreous making vitrectomy easier, faster--easier in some fashion, which was not collected in the present study although, obviously, vitrectomies were done.

Is there a feeling, if you were to go back and look at vitrectomy time, surgical time, would that be reflective of an easier surgical case?

DR. FONG: Do you want a discussion or do you want a vote?

DR. CHAMBERS: I want to know whether there is a general feeling that that would be a useful parameter to look at.

DR. FONG: Dr. Pulido?

DR. PULIDO: I don't think so because the underlying pathology that caused the hemorrhages is as important or more important than the amount of time it takes to get that hemorrhage out of there. So there would be so much data that would have to be looked at retrospectively that it would be very difficult to do. Again, my concern more is is there a negative effect, not if there is a positive effect.

DR. WILKINSON: Pat Wilkinson. I would agree with the answer no for this trial. I would think, based on what the sponsor's consultants said, we would expect removal of blood to be somewhat faster but the guts of a vitrectomy operation in a diabetic patient are the interface between the cortical vitreous and the retina.

It is extensive. You have got a very, very difficult case. If it is simply an insertion on the optic nerve, it is very, very simple. So the essence of the operation and the difficulty of the operation and the length of the operation are going to be much more related to the underlying vitreoretinal pathology than to simply removing the blood.

DR. FONG: Dr. Feman?

DR. FEMAN: I will take the other tack, although Pat is a friend of mine. I disagree with the concept in that I think that there may be something special to offer patients with this in that, if you can reduce the time in the operating room as a hypothetical case, imagine a patient with heart failure and renal failure that you want to just operate on as little as possible because of their danger to them of the anesthesia, whether local or any other type of anesthesia.

This would, perhaps, shorten your operating time by a significant amount. Would that be a benefit that this agent would offer?

DR. WILKINSON: Pat Wilkinson, again. I agree. There is no doubt that it would shorten the operating-room time, but you are talking about, perhaps, one minute versus seven minutes. When the dissection and delamination at the vitreoretinal interface can take an incredibly much larger amount of time.

So the variable of time for this surgery in this indication, I think, would be a difficult study to set up and should probably be limited to very specific indications for the vitrectomy.

DR. FONG: Thank you. Let's move on to

Question 5. "Are there adverse experiences that are of particular concern for this product?" We will start with Ms. Knudson.

MS. KNUDSON: Paula Knudson. I was struck by the amount of pain that people reported. I am unclear and would like more clarification. Does every kind of injection into the eye produce this kind and amount of pain, because I don't know that.

DR. FONG: That is an interesting question. I guess before we answer that, let's have a discussion about that issue. Maybe Wiley and Jennifer can give us maybe some baseline on what you guys think of it. How does it compare, let's say, to Vitravene or gancyclovir injections?

DR. CHAMBERS: Wiley Chambers. Actually, I don't think I am probably the best one to be answering it in this particular case since I am reading the papers from the sponsor. You have people who have actually been in the room with the patients that have received it. I would suggest they are better ones to ask.

DR. FONG: Maybe, Barry, you gave us some data before. Maybe you can sort of tell us again and compare that against gancyclovir injections and so forth.

DR. KUPPERMAN: I may, in fact, have the most experience here with giving injections because of my history of treating AIDS patients with gancyclovir. I saw and I did have a fair number of patients that we have treated with the Vitrase. I saw difference between the responses to the two types of injections. That includes also having done a significant number of triamcinolone injections and other sorts of injections as well for endophthalmitis, et cetera. Endophthalmitis, of course, is typically more associated with pain because of the more inflamed eye, but this is very similar to the sort of site-injection pain associated with either a gancyclovir, foscarnate injection for an AIDS patient or with a triamcinolone injection for a patient with diabetic macular edema.

DR. FONG: Barry, do you remember, sort of, the number or the percentage of pain that was reported for those studies? Do you happen to remember that?

DR. KUPPERMAN: No. Again, this is simply a matter of asking--the patient's complaint and the comment about the pain and the irritation that followed. It was typically similar across all

these types of injections. We do injections on a regular basis, and there was nothing that separated the subset of patients that received Vitrase injections from the patients who received all the other types of injections I have been involved with.

MS. KNUDSON: I was just curious whether it was the injection, itself, or whether it was the drug, itself, that was inducing the pain.

DR. KUPPERMAN: There was no evidence that it was the drug, itself. It was the site injection from the needle stick.

DR. FONG: Dr. Steidl?

DR. STEIDL: My answer is no.

DR. FONG: Dr. Dunbar?

DR. DUNBAR: My answer is yes, I am concerned about the iritis.

DR. FONG: Dr. Feman?

DR. FEMAN: My answer is no.

DR. FONG: I am the sort of a person who likes more information. So, do I have particular concern? My answer would be yes, just until I had more information to understand exactly what is going on with those retinal detachments. Is it related to the injection or not, just sort of more

analysis along those lines.

Also, I am concerned about the issue of pigment and inflammation that Dr. Pulido raised especially if one is concerned about, or one is interested in, injecting in both eyes. Certainly, we would not want to insight a severe inflammation response with injection into the second eye.

Dr. Gates?

DR. GATES: I am interested in the mechanism of action of the hypopyons although I feel like the company has a good handle on what is going on and how to handle and how to follow these folks. I think that is something you are going to see.

DR. FONG: No concern? Okay.

Dr. Brown?

DR. BROWN: Jeremiah Brown. My answer is yes. My basic issue is the saline rate of retinal detachment, 5.8 percent, 55 International units of Vitrase rate was 10.3 percent. If, in fact, it is that the view is clearing, another thing that could be done is to go back and look at those records and look at the patients who never had--who did not have a detachment early but maybe still had vitreous hemorrhage so we couldn't see that.

How about when that hemorrhage eventually cleared? Do those rates start coming up to match each other? That would be one way to look at it.

DR. FONG: Dr. Pulido?

DR. PULIDO: Yes, for the concerns already raised.

DR. FONG: Dr. Wilkinson?

DR. WILKINSON: Pat Wilkinson. A mild yes for the issues that you and Jose brought up.

DR. FONG: Dr. Chew

DR. CHEW: Yes, just for the retinal detachments in particular.

DR. CHEW: Dr. Phillips?

DR. PHILLIPS: No.

DR. FONG: Dr. Tan?

DR. TAN: Yes. I feel that the rate for retinal detachment is too high for me.

DR. FONG: So the tally for Question No. 5 is eight yes and four no.

With no objections, I would like to proceed to Question 6. "Is there a concern about the death rate observed in these studies?" Dr. Tan?

DR. TAN: No. It seems the death rates are comparable to the patient population.

DR. FONG: Dr. Phillips?
DR. PHILLIPS: No, for the same reason.
DR. FONG: Dr. Chew
DR. CHEW: No. We know that patients with proliferative disease have a high rate of mortality. I just hope that the next studies that they take this into account for their power-size calculation because it is significant.
DR. FONG: Dr. Wilkinson?
DR. WILKINSON: No.
DR. FONG: Dr. Pulido?
DR. PULIDO: No.
DR. FONG: Dr. Brown?
DR. BROWN: No.
DR. FONG: Dr. Gates?
DR. GATES: No.
DR. FONG: Donald Fong. No.
Dr. Feman?
DR. FEMAN: No.
DR. FONG: Dr. Dunbar?
DR. DUNBAR: No.
DR. FONG: Dr. Steidl?
DR. STEIDL: No.
DR. FONG: Ms. Knudson?
MS. KNUDSON: No.

DR. FONG: So it is unanimous no to Question No. 6. I would like to go to Question No. 7. "Do the benefits of using Vitrase outweigh the risks in the treatment of vitreous hemorrhage?" I forgot which side I started on. Paula?

MS. KNUDSON: Paula Knudson. I think yes, not the most positive yes, but yes.

DR. FONG: Dr. Steidl?

DR. STEIDL: In view of everything said so far, this is a difficult question to answer. I think I might give a mild yes. We acknowledge the difficulty with statistical significance but both the benefits and the risks are small, so I guess yes, with a few qualifications.

DR. PULIDO: Can I ask a point of clarification? The first question was, has sufficient evidence been submitted to support the efficacy. So if people have voted no for efficacy, can they vote yes for benefits?

DR. FONG: I think, to be consistent, I will defer to Wiley and Jennifer and see what their experience was. It seems like, if you are going to say that there is no evidence submitted, insufficient evidence. It is hard to be consistent and say that there now is a benefit. Scott? Dr.

Chambers?

DR. CHAMBERS: We bring products before the committee because we have not made final decisions. We write questions because we don't know what the vote is going to be ahead of time. So we try and provide the different contingencies. The assumption was that this question is more relevant if the first question comes out a majority of people thinking there is sufficient efficacy and then there is a question of efficacy versus risk.

If there is not felt to be sufficient efficacy initially, then we think it was unlikely that you would come up with a vote that said that the benefits outweigh the risks in the last question, but we were trying to cover the various potential contingencies not knowing how a vote would come out ahead of time.

DR. FONG: Would you like us to poll the yes--no? I hear a no from Dr. Bull.

DR. BULL: Jonca Bull. I guess the committee will have to weigh whether or not there may be some internal contradiction as Wiley has articulated relative to the questions trying to anticipate the contingencies, as he stated. If there is a consensus that the vote on the first

question, on efficacy, it sort of puts you in somewhat of a dilemma here to comment on benefits and risk when the comments we received before don't go in the direction of having established sufficient efficacy. So I will defer to you all as to whether or not you want to pursue responding or to just overall provide some comments.

We are hearing rather tepid responses from the folks who have responded already.

DR. FONG: Wiley, would you accept just an overall discussion instead of a yes/no answer to this?

DR. CHAMBERS: Yes.

DR. FONG: Dr. Pulido?

DR. PULIDO: Since I brought this question up, I would like, then--if people are saying yes for this last one, I would like them to reconsider, then, their vote for the first one.

DR. STEIDL: Let me say something to that. Maybe with more clarification of what we are answering, it would be easier. I take the first question to be something quite specific relative to statistical proof and the last one a letter of the law versus spirit of the law. Is there a time when you would use it where you are thinking maybe you

don't have an alternative, is this a dangerous drug.

I am still not completely clear what the question is asking but, if it is a broader question, I could say very mildly yes, but depending upon how we are approaching it.

DR. FONG: I think there are two issues. Wiley said you don't need to vote yes or no and second is that, if you have specific comments, I think you definitely want to report it so that the company and the FDA knows what the issues are.

DR. CHAMBERS: This is Wiley Chambers. The assumption was that this question would only come up if we decided or if the committee had decided there were sufficient benefits and sufficient efficacy established in what was Question 1. We then asked other questions to get a fuller discussion to try and get additional aspects as far as the analysis.

Remember, the agency will take back all this information and make a determination whether we think the drug should be on the market or not. That is not the question that we are asking, per se. What we are asking for are are there clear benefits that outweigh the risks for the particular

drug in this particular case based on the information you have seen.

We understand and will take in all the various comments and we understand the issues of the individual patients and the other factors that go in with providing treatment. But we are looking at the overall benefits versus the risks based on the data that you have seen presented.

DR. STEIDL: I will say no. I think it is an issue--

DR. FONG: You don't need to say yes or no, just so you know.

DR. STEIDL: All right. I think what this brings up are some interesting issues. First of all, the person who might not be able to have a vitrectomy and a number of other scenarios where, if you had something available where someone was scared of surgery, would you consider using it if you didn't think that the risks were too high.

Again, maybe just as an adjunct to the greater question if you are trying to look to other areas for insights, I think that maybe at face value, this should be linked to Question 1. But I am taking it as a broader question. I think there might be situations where you want to consider

using it I guess is all I can say, if it were available.

DR. FONG: So, to summarize, I think you would say yes you could imagine a situation if it can be shown to be effective.

DR. STEIDL: Right.

DR. FONG: Dr. Dunbar?

DR. DUNBAR: I appreciate Dr. Steidl for clarifying this because the way he expressed it is the way that I feel. This also gets back to the stratification issue. I am very hopeful that we will be able to determine a subgroup of patients that this is helpful for, but in light that I voted no for the efficacy, I would have to vote no the way things stand at this point in time.

DR. FONG: Dr. Feman?

DR. FEMAN: To read the question the way it is phrased, the risks in the treatment of vitreous hemorrhage using this is not really much different than the risk of injecting saline except for the hypopyon and the other things that we find are easy to treat.

The benefits potentially could outweigh the risk of injecting saline but just barely. So I think, to answer this question the exact way it is

phrased, I would say yes even though I voted no on the first portion.

DR. FONG: I agree with what has been said so far which is that the risks are relatively low. However, I am not convinced of the benefit so, if you have a no on the numerator, let's say, or one portion of the equation, then the whole equation would have to be no.

Dr. Gates?

DR. GATES: I would concur. I am also optimistic that there is a subgroup of patients, perhaps a very, very sick group of patients or a fearful group of patients that can benefit from this in the data that I have seen so far.

DR. FONG: Dr. Brown?

DR. BROWN: Yes.

DR. FONG: Dr. Pulido?

DR. PULIDO: Yes, minimally.

DR. FONG: Dr. Wilkinson?

DR. WILKINSON: Yes.

DR. FONG: Dr. Chew

DR. CHEW: I would also say yes. I think that my answer is similar, I think, to what Scott was saying earlier that statistically looking at it in general, it was difficult to give an efficacy.

But I can imagine some clinical situation where I think it would be very useful and there are some patients who may benefit from this.

I am not that a separate analysis can be done in this case. It is such small numbers to begin with that it is always dangerous to go on subgroups, but I am sure there are probably some patients who really are benefitting from this.

DR. FONG: Dr. Phillips?

DR. PHILLIPS: To be consistent with how I voted on No. 1, I am going to say no. But I do think that a specific subgroup, either medically unable to go through a vitrectomy or just literally refuse to go through surgery may benefit. But, looking at the overall group of patients with vitreous hemorrhage, I will say no.

DR. FONG: Dr. Tan?

DR. TAN: I understand we don't have to vote here, but my answer is no, not as presented.

DR. FONG: We have a split vote, six for yes and six for no. Is there anything else that the FDA or the sponsor would like--

DR. CHAMBERS: Nothing from the FDA's perspective except to thank you very much for your time and efforts.

DR. KUPPERMAN: I don't mean to interrupt, but I got seven/five. I'm sorry. I guess I would like to sort of clarify as I was running through my math. I didn't get whether Scott ended up being a yes or a no because that would have made it six/six versus seven/five. I don't know if that matters or not, but when I was doing the tally, I had seven/five. That is the only reason I want to clarify.

MS. TOPPER: According to the records, Scott did change his mind to no; is that correct?

DR. FONG: Scott, what was your vote?

DR. STEIDL: I am a little confused about the question, personally. But I did say similarly--my feeling is similar to what Stephen Feman stated that, although I said no to the first, I am thinking about the last question in a broader sense. So I guess you could put me as a yes. I could clarify that in detail, if you want, but--I think that there probably are subsets and patients where I would consider it so I kind of feel that I would have to say yes to this even though it may seen contradictory.

DR. FONG: Scott, when was the last time you stopped beating your wife? This concludes the

subcommittee meeting of the Ophthalmic Drug Advisory Committee of the FDA. The final vote was seven yes, five no looking at Vitrase sponsored by ISTA Pharmaceuticals. Thank you.

[Whereupon, at 2:45 p.m., the meeting was adjourned.]

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