FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE (DODAC) MEETING

Virtual Meeting

Monday, January 9, 2023

9:31 a.m. to 3:56 p.m.

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P R O C E E D I N G S

(9:31 a.m.)

Call to Order

DR. CHODOSH: Good morning, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Audra Harrison, and her email and phone number should be displayed in a moment.

My name is Dr. James Chodosh, and I will be chairing this meeting. I now call the January 9, 2023 Dermatologic and Ophthalmic Drugs Advisory Committee meeting to order. Dr. LaToya Bonner is the designated federal official for this meeting and will begin with the introduction.

Dr. Bonner?

Introduction of Committee

CDR BONNER: Thank you, sir.

Good morning. My name is LaToya Bonner, and I'm the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. I

will start with our industry representative, Dr. Atillasoy.

(No response.)

CDR BONNER: Dr. Atillasoy, can you hear me?

(No response.)

CDR BONNER: Okay. I will proceed forward to our chairperson.

Dr. Chodosh, can you please reintroduce yourself, and then I will go back --

DR. ATILLASOY: Can you hear me now?

CDR BONNER: -- to you, Dr. Atillasoy.

I can year you now, sir. Go ahead. Yes, I can.

DR. ATILLASOY: Good. Sorry about that. I keep speaking on mute.

CDR BONNER: No problem.

DR. ATILLASOY: Good morning. I'm Dr. Ercem Atillasoy. I'm the chief regulatory safety officer at Jazz Pharmaceuticals.

CDR BONNER: Thank you, sir.

Next, we'll have our chairperson. Please reintroduce yourself, sir.

DR. CHODOSH: Hi. Dr. Jim Chodosh. I'm the chair of Ophthalmology and Visual Sciences at the University of New Mexico and chairperson for this meeting. Thank you.

CDR BONNER: Thank you, sir.

Next, we have Dr. Durham.

DR. DURHAM: Good morning. This is Todd Durham. I'm the senior vice president of Clinical and Outcomes Research with the Foundation Fighting Blindness. I'm the consumer representative.

CDR BONNER: Thank you, sir.

Dr. Murray, please introduce yourself and your affiliation, sir.

DR. MURRAY: Good morning. I'm Dr. Timothy Murray. I represent Miami Ocular Oncology and Retina, in Miami. Thank you.

CDR BONNER: Thank you.

Next, we'll have Dr. Chiang. Please introduce yourself, sir.

DR. CHIANG: Hi. I'm Michael Chiang. I'm director of the National Eye Institute.

CDR BONNER: Thank you.

Next, we'll have Dr. Clayton. Please introduce yourself.

DR. CLAYTON: Good morning. I'm Janine. Clayton, the NIH associate director for Research on Women's Health and the director for the NIH office of Research on Women's Health.

CDR BONNER: Thank you, ma'am.

Next, we'll have Dr. Joniak-Grant.

DR. JONIAK-GRANT: Hi. I'm Elizabeth Joniak-Grant. I'm serving today as the patient representative, and my current affiliation is with the University of North Carolina Injury Prevention Research Center.

CDR BONNER: Thank you, ma'am.

Next, we'll have Dr. Lai. Please introduce yourself and your affiliation, sir.

DR. LAI: Good morning. My name is Dr. Michael Lai. I am a retina specialist with The Retina Group of Washington here in Washington, DC. I also hold a faculty position with Georgetown School of Medicine, and I was formerly the chief of pediatric retina at Children's National Medical

Center.

CDR BONNER: Thank you, sir.

We'll have our FDA participants, starting with Dr. Ganley. Please introduce yourself, sir.

DR. GANLEY: Hi. I'm Charley Ganley. I'm the director of Office of Specialty Medicine in the Office of New Drugs, in CDER.

CDR BONNER: Thank you.

Next, we'll have Dr. Chambers.

DR. CHAMBERS: Good morning. I am Wiley Chambers. I am the director of the Division of Ophthalmology in the Office of Specialty Medicine.

CDR BONNER: Thank you.

Next, we'll have Dr. Boyd.

DR. BOYD: Hi. Good morning. I'm William Boyd. I'm the deputy director, Division of Ophthalmology.

CDR BONNER: Thank you, sir.

I will now turn this meeting back over to our chairperson, Dr. Chodosh.

DR. CHODOSH: Thank you, Dr. Bonner.

For topics such as those being discussed at

this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal for this meeting is that there will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson, myself, and we look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are well aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Bonner will now read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you, sir.

The Food and Drug Administration is convening today's meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in

compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, and when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants,

CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves supplemental biologics license application 125387, aflibercept solution for intravitreal injection, submitted by Regeneron Pharmaceuticals, Incorporated. The supplement was submitted in response to the FDA's pediatric written request. FDA's written request was for studies of aflibercept in the treatment of retinopathy of prematurity. This is a particular matters meeting during which specific matters related to Regeneron's sBLA will be discussed.

Based on the agenda for today's meeting and all financial interest reported by the committee members and temporary voting numbers, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Ercem Atillasoy is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Atillasoy's role at this meeting is to represent industry in general and not any particular company. Dr. Atillasoy is employed by Jazz Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

I will now turn the meeting back over to our chair, Dr. Chodosh.

DR. CHODOSH: Thank you, Dr. Bonner.

We will now proceed with the FDA introductory remarks from Dr. Wiley Chambers.

FDA Introductory Remarks – Wiley Chambers

DR. CHAMBERS: Good morning. On behalf of the FDA Center for Drug Evaluation and Research, Office of New Drugs, Office of Specialty Medicine, and Division of Ophthalmology, I would like to welcome all the members of this advisory committee and all those listening in to the discussion today.

Today we have brought to the committee a supplemental application for EYLEA, also known as aflibercept, for the treatment of retinopathy of prematurity. This is a rare orphan condition in which there is no current pharmacological therapy. We very much appreciate the time spent by the advisory committee staff, advisory committee members, and their expertise that they bring to this meeting in the hope that we can provide a more complete labeling for this potential product when it is introduced into the market.

Again, I cannot minimize how much we appreciate the time that you spent both looking at

the pre-material, as well as your discussion and remarks today. Thank you.

(Pause.)

CDR BONNER: LaToya Bonner, DFO for this meeting. I will now turn the floor back over to our chair, Dr. Chodosh.

DR. CHODOSH: Thank you. Sorry. I believe that I was muted.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the

outcome of the meeting.

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

We will now proceed with Regeneron's presentations.

Applicant Presentation – Boaz Hirshberg

DR. HIRSHBERG: Good morning, Dr. Chodosh, members of the committee, and the FDA. I am Boaz Hirshberg, senior vice president of Clinical Sciences General Medicine at Regeneron Pharmaceuticals. We are pleased to be here today to share the safety and efficacy data of aflibercept 0.4 milligrams for the treatment of retinopathy of prematurity or ROP.

Aflibercept 2 milligrams, also known as EYLEA, is an FDA-approved anti-vascular endothelial growth factor or anti-VEGF injection. It was

originally approved in 2011 for the treatment of neovascular or wet age-related macular degeneration. Since then, it has also been approved for macular edema following retinal vein occlusion, diabetic macular edema, and diabetic retinopathy.

Aflibercept is also authorized for adults in most of these indications in more than 100 countries outside of the U.S., so it's recently approved for ROP in Japan and in the European Union. Let's briefly review the mechanism of action.

The VEGF pathway is well understood, and VEGF plays an important role during normal embryonic vascular development. However, preterm birth can interrupt normal retinal development, which typically completes by 39-40 weeks. When this occurs, the avascularized and ischemic retina upregulates VEGF and other related cytokines.

The overexpression of VEGF can result in pathological neovascularization and increase vascular permeability, key characteristics of ROP.

Once injected, aflibercept binds to VEGF with a very high affinity. This prevents activation of the receptors, halting the formation of abnormal blood vessels and reducing vascular permeability.

Let me briefly review the regulatory history for aflibercept in ROP. Based on the severity of the disease, lack of approved pharmacologic treatments in the U.S., and the potential benefit of aflibercept in ROP, Regeneron received a pediatric written request from the FDA in June of 2019. In agreement with agency, we initiated the ROP program, including two global clinical studies. All study protocols and statistical analysis plans were approved under a special protocol assessment.

In July 2019, aflibercept was granted orphan drug designation based on the rarity of the disease. In August of 2022, Regeneron submitted the sBLA for aflibercept for the treatment of ROP. In October, a pediatric exclusivity extension was granted by the FDA, indicating that all commitments have been met.

The indication and the recommended dose of

aflibercept as shown in the FDA's briefing document is 0.4 milligrams administered by intravitreal injection for the treatment of retinopathy of prematurity.

Turning now to the data supporting this additional indication, despite the severity of ROP, laser photocoagulation is the only FDA cleared treatment in common use, and there are no FDA-approved pharmacologic treatment options. The aflibercept development program for ROP, which includes two adequate and well- controlled clinical trials, was designed to provide another primary treatment option for this severe vision-impairing disease.

We acknowledge that the primary endpoint did not meet the prespecified non-inferiority criteria compared to laser therapy, however, consistent efficacy was demonstrated, and the efficacy data cannot be viewed in isolation. Today you will hear that aflibercept provides meaningful clinical and practical benefit compared to laser therapy, and aflibercept data builds upon data from commonly

used but unapproved anti-VEGF treatment.

Importantly, the positive efficacy comes with an expected and acceptable safety profile in preterm infants. It's further supported by more than a decade of FDA-approved use in adult indications, with more than 50 million doses administered. I want to emphasize that aflibercept will not replace laser treatments for all patients; rather it can act as an alternative initial therapy and can complement later laser therapy for those who may need additional treatment.

We are here today to share the clinical data with the committee and, as FDA notes in your briefing document, discuss the proposed label changes for EYLEA in ROP. Encompassed in FDA's written request for pediatric studies, data from the ROP program will be included within labeling. The label is an important tool to inform physicians of the proper use of dosing of aflibercept for ROP. We have reviewed the FDA's proposed changes to the label and are aligned with their recommendations.

As with any anti-VEGF treatment, aflibercept

requires adjustments in monitoring frequency compared to laser therapy. With approval, proactive education on appropriate patient follow-up could be provided to prescribers. Approval would also allow for regulated pharmacovigilance to monitor and report ongoing safety.

In addition, we recognize the need for long-term follow-up for anti-VEGFs. Such follow-up through 5 years of age is currently underway within the extension studies. We look forward to the committee's discussion today. This will inform our later discussion with FDA on how best to communicate to physicians and caregivers the use of aflibercept in ROP.

With this information in mind, here is the agenda for the remainder of today's presentation. Dr. Faruk Örge will describe the disease background and unmet medical needs. Dr. Robert Vitti will present the clinical efficacy data followed by Dr. Suzanne Green, who will review the safety profile, and Dr. Steve Donn will conclude with his

clinical perspective. We also have additional experts with us today to answer your questions. All outside experts have been compensated for their time in today's meeting.

Thank you. I will now turn the presentation to Dr. Örge.

Applicant Presentation - Dr. Faruk Örge

DR. ÖRGE: Thank you, Dr. Hirshberg.

Good morning. I'm Faruk Örge, a professor of ophthalmology and pediatrics at Case Western Reserve University, and the director of pediatric ophthalmology at Rainbow Babies and Children's Hospital. I was also one of the investigators for the BUTTERFLEYE study. I truly appreciate the opportunity to be here today and share the disease background and unmet medical need for this serious disease. I've been in this field for 18 years, and can honestly say, unfortunately, we still are not where we need to be. An FDA-approved, easy to administer, accessible pharmaceutical treatment with comparable efficacy and safety to current options would be an important advance for infants

with ROP.

Retinopathy of prematurity is a rare, vision-impairing and potentially blinding retinal disease, and while rare, ROP is the leading cause of preventable childhood blindness worldwide, and due to improved survival of extremely preterm newborns, the incidence is increasing. The disease is characterized by incomplete retinal vascularization and pathologically vascularization, and it is most common and usually more severe in babies born before 32 weeks and weighing less than 1500 grams or 3.3 pounds. Let me expand on why and how ROP occurs.

When a healthy baby is growing in utero, the retinal vessels are fully grown by the time the baby is almost full term, which is at about 38 to 40 weeks of gestation or by 8 to 9 months. When the baby is born early, the blood vessels in their eyes haven't finished developing as would be expected.

For example, if the baby is born at 6 months or 24 weeks gestation, the baby's vessels would

only grow to this point. When the babies are in a different environment outside their mother's womb, they may be exposed to severe multisystem problems. Because of this, normal vessel growth may slow and abnormal vessels may grow.

Also, many of the things that premature babies need to survive, such as various medicines, supplemental oxygen, bright light or temperature, can stimulate VEGF production. This can cause abnormal blood vessel growth, and these abnormal vessels are fragile. They can bleed and tear the tissues apart.

Here you see a photograph and angiograph image of a baby's retina with significant ROP. The normal blood vessels stop growing and a ridge is seen separating the vascularized retina from the avascular retina, which is the dark area. In many cases, ROP goes away on its own as an infant grows; however, for babies with severe ROP like the one shown in these images, treatment is needed.

The international classification of ROP provides the mapping of the disease. It helps to

tell us the zone or how far in the eye the normal vessels have grown; the stage to define the severity of the disease; and whether or not we see plus disease, which are significant vascular changes in the posterior pole.

The zone is classified by how far the normal retinal vessels have managed to grow. The retina is divided into three zones. ROP can develop in any of these zones. Zone I ROP, starting in the center of the eye, is the most severe form. There are five stages of ROP, further indicating the severity.

Stage 1 is characterized by a demarcation line between the vascular and avascular retina; stage 2 is where the demarcation line converts to a ridge; and stage 3 involves extra retinal fibrovascular proliferation or neovascularization. We get nervous about ROP when the process advances to stage 3.

We want to apply treatment before the ROP progresses to stage 5. Once ROP gets to these later stages, defined as partial or total retinal

detachment, extensive surgery is often required, and the probability of ROP affecting the vision significantly increases.

Plus disease is when the vascular shunting is so severe in the border of the ROP that the posterior pole veins are enlarged and the arteries are tortuous. In many cases, plus disease is the indication for treatment.

Shown here are examples of mild, moderate, and severe plus disease. Aggressive posterior ROP, or AP-ROP, is an uncommon, rapidly progressing and severe form of ROP. If left untreated, it will usually progress to stage 4 and 5 in a matter of days. In this aggressive form of ROP, the plus disease is seen even in early stages. Among eye surgeons, there is a consensus to use anti-VEGF first-line therapy for this type of ROP, which is now referred to as AR-ROP or aggressive ROP.

It's important to emphasize that many babies may have ROP, but not all will need treatment. If they meet certain criteria, progression to severe ROP is likely, and treatment is warranted. ROP

that meets these criteria is called type 1 ROP and is generally defined as any stage in zone disease with plus disease or stage 3 zone I disease, even without plus disease.

A major goal in ROP treatment is to avoid retinal detachment, extensive surgery, and the risk of vision-related complications and blindness. When the baby gets to type 1 ROP, timely treatment is critical. It must be applied within 72 hours.

Today there are two common treatments for ROP worldwide: retinal laser photocoagulation and intravitreal injection of an anti-VEGF agent. Both options aim to stop abnormal blood vessel growth by decreasing the production or signaling of VEGF.

National organizations such as AAP, AAPOS, and AAO acknowledge off-label use of anti-VEGF, the potential of these treatments, and recommendations for follow-up. There are no anti-VEGF or any other pharmacological agents currently approved in the United States. This leaves only retinal destructive laser therapy or off-label, anti-VEGF options.

Laser therapy is effective, but it comes with challenges, particularly as a primary treatment for preterm babies. Expanding on this, as laser treatment is significantly longer than intravitreal injection, it requires a baby to be under sedation or anesthesia, and the exposure to these agents is increased. The procedure also often requires babies to undergo endotracheal intubation and needs to be in a designated native location for laser application.

Laser requires a lengthy training period due to its complexity. Improper administration can lead to variable outcomes. All of these can limit access to care or require babies to be moved to a specialized setting. It's also important to emphasize that laser treatment is inherently destructive. In fact, destruction actually equates the efficacy. Seen here is an image of a retina that has received laser therapy. Laser burns away the edge of the retina to prevent blood vessel growth, but in doing so it results in loss of peripheral vision and a number of other possible

complications, which could occur immediately or over time.

Studies show a reported 50 percent of patients will eventually develop high myopia at some point in early childhood. Laser burns cause local inflammation due to thermochemical changes. This results in permanent scarring as seen in this image. The bigger the area that requires laser treatment, the more widespread the damage. The younger the baby at the time of the laser therapy, the more destructive it is to the retina since we need to laser a larger area.

For example, for a baby receiving laser at 35 weeks post-menstrual age, we need to laser the entire area seen here in blue. Now, if the baby needs treatment at a later time, let's say closer to 40 weeks, the normal vessels are more developed. At this point, we need to only laser this light blue area. In that case, with less laser applied to the eye, there will be a lower chance of unfortunate side effects such as loss of peripheral vision, high myopia, and/or other problems.

Here you see retinal images of two patients who received laser treatment. The first patient was treated at 30 weeks and the second was treated at 38 weeks of post-menstrual age. In the second patient, significantly less laser treatment was needed, and therefore you see less post-laser scarring.

In addition, as I mentioned, laser therapy is extremely challenging to administer and not always an option for fragile babies. Let me explain what a surgeon must do to perform the procedure.

The surgeon needs to focus laser spot on the retina and move from one target to another, making only very small head movements, all the while maintaining stability of the lens, helping to focus the image of the retina and stabilizing the eye; all the while pressing a pedal with one foot that fires the laser shots one tap at a time.

Hence, it takes a long time to gain the muscle memory and skill to adjust the distance, tilt, and position of the magnifying lens to allow

good visualization of various parts of the retina, let alone to administer the laser perfectly one after another. Then for each eye, the sturgeon must repeat all of this 1500 to 2000 times. The surgeon also must travel around the baby's head to apply the laser to the baby's retina for 360 degrees inside the eyes as shown here.

All of this must be done quickly and efficiently before the eye dries and the view declines. From time to time, the surgeon must break position to administer moistening eye drops, and then regain position. The babies are very fragile, and treatment is paused frequently due to bradycardia, apnea, and defining oxygen saturation.

It also becomes difficult to apply laser around the commonly used mask nasal cannula, CPAP breathing units, and endotracheal tube. And even with the most experienced and trained eye surgeon applying laser, in a relative facility there are many scenarios when laser simply cannot be administered.

The early data prompting off-label use of

anti-VEGFs have been promising, yet preliminary. Two studies have been published, one with bevacizumab and one with ranibizumab, all through randomized, open-label studies comparing anti-VEGF to laser therapy. The BEAT-ROP study looked at bevacizumab, the most commonly used anti-VEGF agent due to its accessibility, though there is lack of consensus regarding the most appropriate dose since the study was published.

This study enrolled 75 patients per group stratified by zone I or II disease. Patients were followed for about 20 weeks. Significant treatment differences were seen between anti-VEGF and laser therapy for patients with zone I ROP but not zone II.

The more recent RAINBOW study assessed different doses of ranibizumab versus laser therapy. Eighty percent of patients in the 0.2-milligram group achieved success at 24 weeks. This data set led to the approval of ranibizumab in Europe.

We need a drug with a well-studied efficacy

and safety profile and well-understood dosing. There are many scenarios, I can assure, where an anti-VEGF treatment is used and preferred to treat a patient with ROP. Anti-VEGF therapy rapidly neutralizes VEGF, which is particularly useful in the treatment of aggressive ROP.

Anti-VEGF treatment is quick. It is a quick procedure often applied with only topical anesthesia. It can be administered at bedside and can be administered even with poor pupil dilation. Since it doesn't destroy the retina, it potentially preserves the visual field, and it leads to less high myopia compared to laser therapy. Basic science suggests that anti-VEGF promotes growth of the normal vasculature while shrinking the growth of abnormal vessels.

Routine training of intravitreal injection is a part of the curriculum of every ophthalmology residency and appropriate fellowship program. Again, laser therapy still has an important place in treatment, particularly as babies get older, but anti-VEGFs have clear advantages in particular as

first-line therapy.

Let me expand on a scenario where anti-VEGF was used in an actual patient. This is a zone I ROP with plus disease that required treatment. The small arrows indicate the border where the vascular zone ends and a vascular zone starts. Right along that border, the red thick line indicates significant neovascularization. Also note the dilation of veins and tortuosity of the arteries. It is still somewhat difficult to see the details due to the underlying pink tissue that masks the contrast, so here is an angiography of the same patient, providing a better visual.

Bright wide structures at the border are all significant neovascularization. We injected an anti-VEGF agent into the eye. This angiography shows the patient's eye one month after anti-VEGF treatment. Note that the normal retinal vasculature has grown, neovascularization has completely disappeared, and plus disease has also regressed with no tortuosity seen in the arteries anymore.

Due to published data and the practical advantages we see with anti-VEGF treatment, U.S. physicians are utilizing more and more off-label anti-VEGF treatments. In fact, off-label anti-VEGF is replacing laser as the primary treatment for ROP. In a 2019 study, using data from the Vermont Oxford Network of more than 380,000 very low birth weight infants across more than 800 U.S. participating in NICUs, they saw a significant increase in anti-VEGF treatment over the past 10 years.

I'd like to emphasize that this large clinical study was done not by ophthalmologists, but by neonatologists, and it confirms what I have seen in clinical practice; that both specialties are collaborating in treating these very critical babies, and frequently agreeing that anti-VEGF should be the first line of therapy. The entire treatment algorithm is under the oversight of the NICU. Together, they decide what treatment, if any, is best for the baby.

Here is another publication showing the same

trends, in this case, the rise in anti-VEGF treatment over 10 years in 27 U.S. states. While fewer babies were treated for ROP in 2020, the percentage of anti-VEGF treatment compared to laser remains prominent. We know that the growth of the normal vessels could be at a different pace after the anti-VEGF treatment. For this reason, babies tend to need longer term frequent follow-up compared to laser. The baby needs to be followed to rule out reactivation or until their retinal vasculature is matured.

The subset of babies whose vessels do not mature, even given time, will end up needing laser as definitive treatment, even without a reactivation of disease. For this reason, an appropriate follow-up has to be performed after any treatment, including anti-VEGF treatment. Follow-up is recommended in current treatment guidelines, as well as in the common practice of the ROP community. Just like how we do it in my institution, the neonatology team, as well as the ophthalmology team, reviews the importance of

appropriate follow-up with families, which may vary from baby to baby. We provide written instructions, including the disease process information, and follow up logistical details.

To conclude my presentation, in view of current data, there are clear benefits to having a regulated, FDA-approved pharmaceutical ROP treatment option that offers meaningful benefits without the associated challenges of laser therapy. Physicians and parents alike truly want and need a well-studied, well-characterized anti-VEGF product with efficacy and safety data that builds on our current evidence.

Approved labeling of such a product will provide physicians with consistent information for use, post-administration monitoring, and improve access for this most vulnerable patient population. It's been too long since we've had approved advances in the treatment of ROP, and they are certainly needed.

Thank you. I'll return the presentation to the sponsor to review the clinical data.

Applicant Presentation - Robert Vitti

DR. VITTI: Thank you, Dr. Örge.

I'm Bob Vitti, vice president of Clinical Sciences and Ophthalmology at Regeneron. I'll share the efficacy data demonstrating aflibercept's clinically important benefit in the treatment of ROP.

The program is supported by two phase 3, multicenter, randomized, two-arm, open-label clinical studies that assess the efficacy and safety of intravitreal aflibercept versus laser. Both studies were global, and BUTTERFLEYE included sites in the United States. Patients were followed through 52 weeks of chronological age. These studies also include observation through 5 years of chronological age to assess long-term safety.

In the BUTTERFLEYE study, infants with ROP were randomized 3 to 1 to either open-label aflibercept or laser photocoagulation therapy. Patients were followed with frequent mandatory visits through 24 weeks after treatment and infants reached 40 and 52 weeks of chronological age with

primary endpoint assessment occurring at 52 weeks of chronological age. Investigational site staff included an ophthalmologist, a neonatologist, and the neonatal intensive care unit team.

Retreatment with randomized therapy or rescue therapy was allowed and captured throughout the study. The FIREFLEYE and FIREFLEYE NEXT study had a similar design, though here patients were randomized 2 to 1. FIREFLEYE was initiated for European submission with a 24-week primary endpoint. For FDA submission, data from FIREFLEYE were combined with data from FIREFLEYE NEXT through the week 52 chronological age visit. Therefore, all analyses shown were conducted on the 52-week endpoint, and moving forward, we'll simply refer to this study as FIREFLEYE.

Infants were enrolled with a gestational age at birth of 32 weeks or younger or a birth weight less than or equal to 1500 grams. Weight at baseline needed to be at least 800 grams for patients to be treated. In accordance with international guidelines, patients had to be

treatment naive with the ROP classification shown here in at least one eye. If only one eye was treated at baseline, the second eye was kept under observation. Second eyes that developed type 1 ROP received treatment according to the same randomized assignment.

Now moving to endpoint selection, the same endpoints were used in both studies. The primary efficacy endpoint was the proportion of patients with the absence of both active ROP and unfavorable structural outcomes at 52 weeks chronological age based on the investigator's assessment. Secondary endpoints included the proportion of patients requiring intervention with a second treatment modality and the proportion of patients with a recurrence of ROP.

We additionally assessed relevant exploratory endpoints important to patients and families such as the need for sedation and the time to perform treatment. Total sample size for both studies was extensively discussed with the FDA, and the rarity and severity of the disease drove sample

size considerations. FDA agreed that 150 infants treated with aflibercept across two studies would be adequate for assessing safety and tolerability, given that safety has been previously established in a large adult treatment population.

We chose a non-inferiority design as the pragmatic way to establish efficacy within the given sample size, and this design is the most appropriate when comparing two treatments with evidence of effectiveness. The prespecified statistical analysis for our studies focused on the difference in response rates between aflibercept and laser.

We set a conservative non-inferiority margin of 5 percent, informed by the treatment effect of ranibizumab versus laser observed in the so-called RAINBOW study. The study compared 2 doses of IVT ranibizumab versus laser in the treatment of ROP and showed a laser success rate of 66 percent and anti-VEGF success rate of 80 percent. For this analysis, a two-sided significance level was set at 0.049 after adjustment for IDMC assessments.

Now turning to demographics, infants in both studies were approximately equally split between males and females. Infants were mostly white and Asian in accordance with site locations. The studies also enrolled infants of black, Native American, and multiple racial descent. The average gestational ages were around 26 to 27 weeks, and the babies were treated, on average, about 9 to 11 weeks later. Average birth weight was well below the 1500-gram enrollment criterion.

As would be expected, infants were mostly treated for bilateral ROP, with few patients in each study receiving treatment for only one eye. The majority of babies had zone II ROP in both studies. Infants with a level of prematurity seen in these studies presented a baseline with a range of serious non-ocular conditions, as would be expected in this population.

Other than prematurity and low birth weight themselves, here are the most commonly reported baseline medical conditions, and they include bronchopulmonary dysplasia; respiratory distress;

infantile apnea; patent ductus arteriosus; and neonatal anemia.

In reviewing the disposition, we see that more infants received their assigned treatment in the aflibercept arm compared to laser therapy. First in BUTTERFLEYE, 127 infants were randomized. One baby in the aflibercept group and six in the laser group withdrew upon receiving randomized assignment; therefore, 99 percent of infants received randomized aflibercept compared to 82 percent of infants who received randomized laser therapy, and 93 percent of babies on aflibercept compared to only 79 percent of babies on laser completed the 52 weeks.

For FIREFLEYE, we see similar discontinuations upon receipt of open-label, randomized assignments. 118 infants were randomized and 5 infants withdrew before receiving laser therapy. Eighty-eight percent of infants on aflibercept compared to 79 percent on laser completed the FIREFLEYE study.

Now moving to the results, as a reminder,

the primary endpoint was based on the proportion of infants with the absence of both active ROP and unfavorable structural outcomes at 52 weeks of chronological age. As you can see numerically, the proportion of infants who reached success was similar between both studies and both treatment arms, around 80 percent.

For context, when adding in the ranibizumab data from RAINBOW, you see very consistent outcomes across anti-VEGFs, and interestingly, the laser group in our studies exceeded historic outcomes observed in the RAINBOW study. In BUTTERFLEYE and FIREFLEYE, treating investigators were very experienced in laser photocoagulation and our studies utilized imaging of the retina using fundus photography, which aided the treating physicians and clinical confirmation of complete administration of laser.

Turning now to the primary endpoint which looked at the success rate difference between arms, the difference in response rates between the two groups, as shown here, is nearly zero. However,

the lower bound of the confidence interval extends below the prespecified, non-inferiority margin of negative 5 percent, and therefore non-inferiority cannot be concluded. We also cannot conclude inferiority or superiority of either treatment. So ultimately, we must consider the benefit-risk of aflibercept, and importantly, that benefit-risk must be placed in the context of current standard of care.

Moving now to secondary endpoints which inform the benefit-risk profile and are provided for descriptive purposes, less recurrence was observed with laser treatment compared to aflibercept with an adjusted difference of 10 percent in BUTTERFLEYE and 3.6 percent in FIREFLEYE, and these recurrences mostly occurred within 6 months of the first treatment in either arm. Recurrence did not necessarily equate to treatment failure, and babies with recurrence were still able to have successful outcomes independent of retreatment.

These recurrences are not unexpected given

the pharmacokinetics of aflibercept compared with the ablative effect of laser. The important point to consider is that in the clinical trials, as in clinical practice, patients continued to be monitored throughout at least their first year post-treatment, and the importance of this follow-up will be communicated to providers.

In situations when the ROP either worsened or didn't respond to initial treatments, patients received a second treatment modality, which was any treatment other than randomized assignment. This signaled failure of the primary treatment to fully regress the ROP, and comparable proportions of babies in both studies required a second treatment modality. Patients in the aflibercept group mostly received laser as a secondary modality, and those in the laser group mostly received aflibercept.

Now, an additional endpoint of interest is to look at aflibercept infants who needed laser rescue treatment. You can see in both studies, most babies, 86 percent in BUTTERFLEYE and 93 percent in FIREFLEYE, did not require laser

rescue; and of those patients who received laser after aflibercept, most had favorable outcomes at the week 52 study visits.

Here are babies in the aflibercept arm in both studies that needed sedation or anesthesia. Now, this is an important exploratory endpoint, as there are safety concerns with placing premature babies under sedation or anesthesia, particularly for longer lengths of time, and when we look at the time to perform treatment, we see a dramatic difference between laser and aflibercept administration.

Shown here is the mean time by participant and by eye for each study, with laser in gray typically taking longer than an hour per eye to administer compared to aflibercept injection, shown in blue, which takes about 5 minutes per eye or less. This is extremely important when we consider time under sedation or anesthesia, which, as Dr. Örge described earlier, places babies at increased risk but also requires proper equipment, monitoring, and care by hospital staff.

In summary, the development program provides evidence of the clinical benefit of aflibercept 0.4 milligrams for the treatment of ROP, especially when compared to laser therapy, which comes with challenges in administration and associated risks. Approximately 80 percent of infants in the aflibercept groups met the primary endpoint in both BUTTERFLEYE and FIREFLEYE. The aflibercept group was numerically similar to those receiving laser therapy. While the lower bound of the 95 percent confidence interval did not meet the non-inferiority margin that was prespecified, the point estimate demonstrated efficacy.

Importantly, secondary and exploratory endpoints emphasize the value of having a pharmacologic treatment, particularly one that will require less time under sedation or anesthesia for these vulnerable premature babies.

Thank you. I'll now turn the presentation to Dr. Green to share the safety data.

Applicant Presentation - Suzanne Green

MS. GREEN: Thank you, Dr. Vitti.

I'm Suzanne Green, a therapy area head of ophthalmology in Global Patient Safety. Today I'll present data showing that the clinical development program demonstrated a favorable, well-tolerated safety profile with expected mostly mild and transient adverse events observed in infants treated with aflibercept.

This slide summarizes the extent of exposure to aflibercept in both of the randomized treatment arms. Across studies, 168 infants were randomized to aflibercept compared to 65 infants to laser, consistent with an unbalanced randomization between aflibercept and laser. The majority of infants treated with aflibercept received a single treatment in both eyes across studies.

Overall, rates of treatment-emergent adverse events were comparable between the treatment arms in both studies. These events were defined as those that occurred within 30 days after the last administration of study treatment. The incidence of serious adverse events was lower in the aflibercept than laser group in both studies.

Treatment-emergent serious adverse events were equal or fewer in the aflibercept group than in the laser group.

There were 4 infants who died in the aflibercept group. None were considered related to treatment. I'll review these cases shortly, and the narratives are included in your briefing document. For context, reports of deaths in this patient population are not unexpected, as there is a range of severe comorbidities associated with very premature birth. In the 24-week RAINBOW study, for example, there was a reported death rate of 5 percent.

Turning now to ocular events, the most common ocular treatment-emergent adverse event was retinal detachment, which occurred with similar frequency in both treatment groups in both studies. Retinal detachment is a known complication of ROP and is considered an unfavorable structural outcome. Conjunctival hemorrhage occurred more frequently in the aflibercept group than laser group. This is an expected event following an

intravitreal injection procedure.

These events were generally non-serious, required no intervention, and resolved spontaneously. Retinal hemorrhage occurred slightly less often in the aflibercept than in the laser group. Conjunctivitis was reported more often in the laser group. It is important to note there were no cases of endophthalmitis reported in any group. Eyelid edema was more frequent in the laser group, possibly related to the longer procedure time.

Next, I'll review the serious adverse events. Ocular treatment-emergent serious adverse events were reported at equal or lower rates in the aflibercept arm across both studies. The most common serious adverse event in both treatment arms was retinal detachment. Serious vitreous or retinal hemorrhage occurred in three and two patients, respectively, in the aflibercept group of the two studies and is an expected complication of ROP or treatment.

Non-ocular treatment-emergent adverse events

were somewhat less frequent in the aflibercept group than laser group. As expected in this very premature population with often extremely low birth weight, the most frequently reported events are respiratory, gastrointestinal, or hematological in nature.

Bronchopulmonary dysplasia was reported in the aflibercept group only, whereas infantile apnea, bacterial disease carrier, and subcutaneous hemorrhage were reported more often in the laser group. Anemia, apnea, constipation, and oxygen saturation decreased were also more frequent in the laser group. Overall, most events were mild to moderate in severity and resolved, or were resolving without a change in study treatment or discontinuation.

Non-ocular series TEAEs were higher in the aflibercept group in BUTTERFLEYE, whereas they were lower than laser in FIREFLEYE. Apnea and infantile apnea were the most common treatment-emergent serious adverse events reported. The vast majority occurred in the laser group. This was possibly

related to the sedation and anesthesia requirements of the procedure, as well as the long procedure time.

At this time, I will now review information around the deaths. One death occurred in BUTTERFLEYE and three in the FIREFLEYE study. Three of the babies were female and one was male. As you can see, these were very premature babies. The gestational age and weight in three of the four babies was well below the mean birth weight of 880 and 990 grams, and mean gestational age of 26.5 to 27.3 weeks seen in the overall study population.

In addition, these babies had very complicated medical histories. The baby in the BUTTERFLEYE study had a laparotomy for necrotizing enterocolitis, which showed massive bowel adhesions 15 days prior to study entry. Seven days prior to study entry, she developed wound dehiscence and developed several entero-cutaneous fistulas. Following this, she remained critically ill with respiratory, intestinal, and renal failure. On study day 29, she experienced multiple system organ

failure and a Klebsiella infection, and died on day 59.

The second baby experienced an exacerbation of pre-existing bronchopulmonary dysplasia on study day 142, which led to intubation and mechanical ventilation. On study day 144, she developed a tension pneumothorax, and died. The third case had a medical history, including neonatal respiratory distress syndrome, bronchopulmonary dysplasia, and 4 episodes of sepsis. On day 53, she developed mycoplasma pneumoniae bronchiolitis, and died 4 days later.

The final reported death had a medical history, including bronchopulmonary dysplasia; respiratory failure; apnea; perinatal brain damage; atrial septal defect; and severe anemia. On study day 61, she developed an exacerbation of pre-existing bronchopulmonary dysplasia, and died the same day. The independent data monitoring committee agreed with the assessment by the investigational team, including ophthalmologists and neonatologists, that no deaths were deemed

related to aflibercept.

To conclude, the safety profile observed in the clinical development program was consistent with the known and favorable safety profile of aflibercept. The safety database provides data on 325 treated eyes in 168 infants treated with aflibercept . Adverse events were mostly mild and comparable to the standard of care treatment. Serious adverse events were less common in the aflibercept arm than the laser arm and are generally consistent with complications observed in very premature infants of extremely low birth weight.

Deaths were infrequent, occurred in patients of complicated medical history and severe comorbidities, and were deemed unrelated to study drug by investigators. Additionally, we recently provided the agency with a safety update report. There were no additional deaths or treatment-emergent serious adverse events reported, and the overall safety profile remains unchanged.

Both data through week 52 were comparable

between aflibercept and the laser group with age appropriate increases. Additionally, two-year follow-up data from the RAINBOW study showed comparable outcomes in growth and neurocognitive development parameters between ranibizumab and laser. Regeneron is also committed to following these infants out to 5 years of chronological age to assess longer term safety data.

Thank you. I'll now turn the presentation to Dr. Steve Donn to share his clinical perspective.

Applicant Presentation - Steven Donn

DR. DONN: Thank you.

I'm Steven Donn, a neonatologist and professor emeritus of pediatrics from the University of Michigan. I've been a neonatologist for 42 years, all at C.S. Mott Children's Hospital.

Laser therapy has been the mainstay of treatment for ROP for decades, but it can be difficult to administer and destroys parts of the retina. This can lead to later visual complications. Those of us who have spent years

practicing in this field have always understood that other options are needed for our patients.

Specifically, we need a therapeutic agent that could work comparably to laser therapy but with fewer side effects. Having an approved option with appropriate labeling would provide physicians and parents more timely access to an effective treatment and the information they need to best care for these premature infants.

The goal of treatment for ROP is to prevent blindness. It is also to leave our babies with as much normal vision as possible. Laser therapy is the only FDA cleared treatment for ROP in common use today, and it is effective, but it comes with practical and clinical limitations. As Dr. Örge shared, there are challenges associated with laser administration. Laser requires specialized equipment and skill to administer properly, and it is not always locally accessible.

To receive laser treatment, vulnerable babies almost always have to be moved from the intensive care unit to other locations. As you can

imagine, this is less than ideal for a critically ill, unstable baby. Removal from the NICU exposes the baby to the risks of hypothermia, hypoxia, hypotension, and dislodgement of critical life support equipment, and it requires additional healthcare personnel. Laser treatment also requires a long duration of sedation and/or anesthesia. Perhaps most impactful, laser therapy comes with the potential loss of peripheral vision and risks of permanent complications like high myopia.

These limitations are primarily why anti-VEGF treatments, including aflibercept, have been increasingly used for ROP even though they are not FDA approved. Anti-VEGF use is included in present treatment guidelines because these compounds show promising efficacy and safety. The aflibercept clinical trials contribute additional data to further substantiate the use of anti-VEGF therapy in the treatment of ROP.

Let's examine the clinical considerations that support aflibercept in ROP. First, ROP is a

rare and serious vision-impairing disease that occurs when babies are often in their most critical state. Secondly, anti-VEGFs are already used off label as a primary initial treatment for ROP due to the limitations and complications of laser therapy. As discussed earlier, the aflibercept studies did not meet the efficacy threshold set, however, the risk-benefit ratio of aflibercept cannot be determined in isolation, but rather must be considered in context with laser, the only currently FDA clear treatment option.

Aflibercept offers consistently high success rates through 52 weeks. Particularly important to treating physicians and families is the much shorter time to administer aflibercept compared to laser therapy, less than 10 minutes versus more than two hours on average. This dramatically decreases the time under sedation, which can substantially reduce unnecessary consequences for patients.

Aflibercept would enable earlier treatment of vascular proliferation than laser. Moreover, it

can be administered at the bedside, obviating the need to move the baby from the intensive care setting. Aflibercept would also offer an option when laser is not feasible, and postponing laser even by one month could preserve more of the baby's visual field and reduce the risk of high myopia.

The safety profile aligns with my expectations. It is comparable to laser therapy, and as an initial treatment, aflibercept comes with the potential for less risk of short-term side effects and long-term complications. Approval of an anti-VEGF would not replace laser therapy entirely. As is already practiced clinically, aflibercept could be used as a primary treatment when laser is not possible or when the complications of laser would be too great.

When I look at the data from these studies, I see clinical benefit. When discussing treatment with a patient's family, my primary focus is on these clinical considerations rather than a single statistic. Instead, I talk about potential treatments to try to preserve their baby's vision.

To conclude our presentation today, it is gratifying to see pivotal prospective data that substantiate and expand our earlier understanding of anti-VEGF treatments for ROP. Aflibercept stops ROP and preserves the retina. The aflibercept clinical program demonstrating safety and efficacy builds on the knowledge already generated by off-label, anti-VEGF use in prior clinical trials.

Approved labeling of an anti-VEGF compound would lead to proper education for use and safety surveillance, something currently lacking in the context of off-label use. Approved labeling of aflibercept for treating ROP would reduce the variability in treatment by providing a recommended dose, dosing interval, and post-administration monitoring. Under the off-label paradigm, currently, anything goes.

I've reviewed the FDA suggested label and feel strongly that physicians and caregivers would benefit from having this label on the product. Approval with the FDA proposed labeling will be an important step towards meeting the unmet medical

need to provide a safe, effective, easy to administer, and, importantly, an approved bedside treatment for our preterm babies. Thank you.

DR. HIRSHBERG: Thank you, Dr. Donn.

This concludes our presentation. We are now open for questions.

Clarifying Questions to Applicant

DR. CHODOSH: Thank you.

This is Dr. Chodosh again. We will now take clarifying questions for Regeneron. Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon again after you have asked your question. When acknowledged, please remember to state your name for the record before you speak, and if possible, direct your question to a specific presenter. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all

for my questions," so we know to move on to the next panel member.

It looks like we have a question from Dr. Joniak-Grant, and I apologize if I in any way mispronounced your name. Please go ahead.

DR. JONIAK-GRANT: Thank you. That's alright.

Dr. Elizabeth Joniak-Grant. I have two questions. The first one is, does the risk profile change at all with more injections per eye, or is it kind of difficult to say much, meaningful, because of the small amounts of the groups getting the 2 injections? I think it was around 14 to 17 percent of the sample for 2 injections and about less than 3 percent for 3 injections per eye. So that's my first question.

Then my second question is that in the briefing documents, it said that if the patient data wasn't available for follow-up at the 52-week chronological age, then data was used from their week 40 visit for analysis. What percentage of participants did this happen for, where you didn't

have the week 52 information and had to use the week 40?

DR. HIRSHBERG: Thank you. Dr. Vitti will address those questions.

DR. VITTI: Bob Vitti, Regeneron. As you point out, there are just too few patients who needed multiple injections to draw any conclusions based on safety outcomes.

The second question, how many patients reached 52 weeks of chronological age, or conversely, how many patients were cut off at week 40, the answer is very few patients actually had data carried forward from week 40 to week 52. The exact number I think we'll have to look up for you during the break.

DR. JONIAK-GRANT: Okay. Thank you.

DR. CHODOSH: Thank you.

Dr. Joniak-Grant, if you're done, we will proceed to the next question from Dr. Michael Chiang.

Dr. Chiang?

DR. CHIANG: Thank you very much for the

presentations. This is Michael Chiang from National Eye Institute. I have two questions, and they're really for the entire panel, probably Dr. Vitti, initially.

My first question deals with the definition of active ROP in the study design. I have a little bit of concern about that with the rationale being that I think there's a lot of inconsistency in terms of to call things when eye disease comes back. In fact, in the ICROP III classification system, that was one of the main motivations for redoing the classification.

I was the chair of the ICROP III committee, and there were several people. Dr. Örge played a big role in convening that, and Andreas Stahl, and Wei-Chi Wu, and Domenico Lepore I know were FIREFLEYE investigators, and they were on the ICROP III panel.

The question is what to call these when it comes back, and we came up with this term "reactivation" meaning that something comes back. And my specific concern is that the term "active

ROP" is much more specific than reactivation. My understanding is that active ROP in FIREFLEYE meant that some disease that was judged to need treatments came back, which I don't think is the same thing as reactivation of disease. So my first question is that I would be interested in your thoughts about how that distinction should be communicated to people because I think that may have implications for follow-up and just level of concern.

My second question is related to that, which is that it was alluded to in several of the comments that there's a need for closer follow-up and a potential need for ablation, either with recurrence of disease, or reactivation of disease, or with development of what's called "active ROP" in the FIREFLEYE and BUTTERFLEYE studies, which I don't believe is a standard term anymore. But I think the question is that I don't feel that there is consensus in the community about how frequently babies need to be followed up and what the threshold for treatment of reactivated ROP should

be, and also whether babies should be treated if the retina does not fully vascularize, which happens really frequently in these babies.

So I would love your thoughts about what guidance specifically should be given to ophthalmologists that's really prescriptive rather than leaving it to people's individual judgment, so thank you very much.

DR. HIRSHBERG: Yes. We would like to have Dr. Örge address those two questions.

DR. ÖRGE: As Dr. Chiang alluded to, the important details of the definition that really applies to the guidance of the community and when do you treat or when do you -- so first of all, I would like to remind the panel that the study was designed prior to the ICROP III publication that came out, so even the AP-ROP now we're calling the A-ROP, and similar things were not defined. So with all this, I think this is a very important factor, as you had alluded, and I think I agree that this definitely needs to be discussed in how to include appropriately in the labeling down the

road after the approval, possible approval, of the medication, and I think the same thing goes along with the guidance.

I know that the company, Regeneron, and the study personnel really have looked at the AAP guidelines, and we know, as Dr. Chiang alluded to, that, anyhow, the community, what we know about the disease is still evolving. So from what I understand, the company will be very lenient on the general consensus on what the wording needs to be on the guidance. But as a physician, individually, I really do think that these very much may differ from case to case.

So really, I would caution on a very specific, as Dr. Chang had alluded, definition on when to treat, but it has to be somewhat case to case, and I think that needs to be acknowledged as well in these discussions going forward. Thank you.

DR. CHODOSH: Dr. Chiang, your hand is still raised. Did you have anything to follow up with?

DR. CHIANG: No, I'm sorry. I'm about to

lower my hand and just say thank you for those comments. I would definitely agree that one of the challenges of this is that ICROP III came after these studies were designed.

Just for disclosure, I personally use anti-VEGF in these babies, and I believe that there are benefits, but one of the challenges is that I think that the community would, in my opinion, benefit from some guidance about when to worry post-treatment and when babies need laser ablation treatment. So thank you very much.

DR. CHODOSH: Thank you.

Next, Dr. Murray, your hand was raised, and now it's down. Do you have a question?

DR. MURRAY: I do. Thank you.

Dr. Tim Murray from Miami. I'm concerned with the high failure rate for anti-VEGF with the use of aflibercept, and I would like to have some clarity as to the dose evaluation. For patients utilizing off-label bevacizumab within our community, the failure rate is under 5 percent, and I do believe that there is concern within the

community that the selected dose of 0.4 milligrams is below what might be the most appropriate dose. So I'd be interested in the discussion of the dosing strategy and why a higher dose was not considered or evaluated. Thank you.

DR. HIRSHBERG: Dr. DiCioccio will address that question.

DR. DiCIOCCIO: Thank you. Thomas DiCioccio, Regeneron Pharmaceuticals. The dose was selected based on a number of independent assessments. First, we took into account a number of ISS studies that have studied aflibercept in the ROP populations, ranging from 0.4 to 1 milligram. Collected across dose studies, there was really no advantage seen as we went from 0.4 to 1 in those studies, and obviously we were interested in maintaining the lowest effective dose possible.

The other point to consider is when you look at the volume of the eyes, the ROP patient population, they were about 20 to 25 percent the volume of an adult eye, say, with AMD; therefore, the 0.1 milligram -- or 0.1 mL -- sorry -- the

10 microliter 0.4 milligram dose represents a similar volume to eye volume and milligram to eye volume as the 2-milligram dose. And while we cannot be assured that a dose across several indications is the appropriate dose, there is a body of evidence that this milligram per eye volume concentration has proven to be very effective, and therefore was selected as a dose to be studied here.

DR. MURRAY: Dr. Murray, again, for a follow-up. Then I would suggest that the VEGF release for neovascular AMD and for retinopathy of prematurity with active threshold disease may be different, and therefore precludes the assessment of volume to volume. And I did believe that there was a small study that evaluated aflibercept comparing the 0.4-milligram and the 1-milligram dose, and though the numbers were small and there was no statistically significant difference, it was interesting that every eye treated with 1 milligram had a response, while there were significant failures to respond in the 0.4-milligram dose.

So I remain concerned that this success rate of 80 percent is below the success rate that would be achievable with a higher dose and is below the success rate that we achieve utilizing an off-label anti-VEGF, bevacizumab. Thank you.

DR. DiCIOCCIO: Yes. Tom DiCioccio again; allow me to follow up with that.

You're absolutely correct. The systemic pharmacokinetics observed with aflibercept do show that there are higher concentrations at a faster rate than in the AMD population, but I also would point to that in the RAINBOW study, they saw exactly the same phenomena with ranibizumab, and that the ratios were just about the same, and the slopes of the clearances were quite comparable as well across those two studies. Unfortunately, I don't have any data on bevacizumab to speak directly to that, but this is a common feature for at least the ranibizumab and aflibercept compounds.

DR. HIRSHBERG: And we would like to ask Dr. Örge to address some of the comments about the success rate across different agents and studies.

DR. ÖRGE: Faruk Örge again, ophthalmology. When we look at, at least, prospective comparative studies like RAINBOW and the BEAT-ROP, it seems like the success rate of the anti-VEGF treatments are very compatible with what we've seen with the aflibercept, and with a very similar population, too, so we believe that it seems like the results that we're seeing is adequately represented. Thank you.

DR. CHODOSH: Thank you. This is Dr. James Chodosh again. I actually have two questions. I'm going to ask them in turn, one, and then after hearing back.

One question was just a question about how the studies were done and how much time elapsed between the initial examination, the randomization, and the treatment, and how that might have compared between the laser and aflibercept; did needing to organize the laser treatment, in other words, lead to perhaps a longer time between diagnosis and treatment, or were the times to treatment from the initial examination equivalent?

DR. HIRSHBERG: Dr. Vitti?

DR. VITTI: Bob Vitti, Regeneron. So there were, on average, about only 3 days from the time of screening to the time of baseline treatment.

DR. CHODOSH: Thank you. Dr. Chodosh again. Did that differ between the treatments?

DR. VITTI: No, it did not. It did not.

DR. CHODOSH: Alright. Thank you. It's Dr. Chodosh again. I'm going to ask my second question. It's actually two, but they're really the same question.

What determines the decision that a baby needs what you refer to as laser rescue? And if we could project, if all babies received anti-VEGF at diagnosis, what proportion of those babies would then need this laser rescue, as it was called?

DR. VITTI: Bob Vitti, Regeneron. The proportion of patients in the aflibercept treatment group that required laser rescue was 14 percent in the BUTTERFLEYE study. In the FIREFLEYE study, it was somewhat less, 7 percent. So one would expect that those proportions would translate into a

larger population.

DR. CHODOSH: I guess my question is, how was that determined? Was that the individual investigator's decision that they should go to laser, or what were the criteria by which they decided that an infant needed, to use the word, "rescue?"

DR. VITTI: Right. Patients who originally randomized to aflibercept were allowed up to 3 injections per eye before it was decided, if they still had active disease, that they needed a rescue. Now, we also insisted on a certain interval in between injections of 28 days, so it's possible -- it was possible, and happened -- that patients who were originally injected with aflibercept recurred in the time frame before another injection was allowed, and therefore those patients would have been automatically rescued by laser, with laser.

DR. CHODOSH: Okay. One of the things that was pointed out and that I also was interested in was the relatively higher rate of success with

laser than in prior studies, and as was mentioned, my guess was that the practitioners had become better at it; and I wonder if you have any thoughts on what will happen if the majority of babies are treated with aflibercept. Do you expect that laser therapy efficacy may drop because practitioners are doing what would be less of it?

(Crosstalk.)

DR. HIRSHBERG: Dr. Örge will address that.

DR. ÖRGE: Faruk Örge again, ophthalmology. As one of the investigators, I have to say -- and I think this is very much one of the reasons why the success rate was different, and particularly from the RAINBOW study -- that prior to this study initiation, all the investigators got together and really defined how the laser treatment needed to be done. So I think that, first of all, gave a little comprehensive understanding and homogeneity.

The second aspect of that is after the laser treatment, photography had to be done to demonstrate the completeness and the appropriateness of the laser, which is, again,

another factor; that as a clinician I know that many times you do the laser and you think you've done the entire area, you take a picture, and you see these skipped areas. I think this really helps the completeness of the treatment, and there suspecting these two factors have been why you're seeing the good result. And again, these sites are sites that actually have good experience with ROP, and particularly laser, as you alluded to, so the community, probably the laser treatment, and the success is probably not as high.

Now coming back to any anti-VEGF, particularly if aflibercept is approved, I truly don't believe that the laser treatment is going to go away. For many aspects, the laser treatment will be necessary if, for the patients who have received this treatment, the vascularization has not fully matured, or as you mentioned, there is -- few but they're there -- reactivation, and some of the babies progress despite the fact that they've received the appropriate treatment.

So the laser treatment needs to be there,

and I think continues to be valid, but probably not in a more vulnerable patient population but better planned and when the babies are a little bit older, is what we're going to see.

DR. CHODOSH: Thank you. This is Dr. Chodosh again. That answers my question.

The next question is from Dr. Michael Lai.

DR. LAI: Thank you. This is Michael Lai. As a number of speakers have pointed out here, eyes treated with anti-VEGF therapy have delayed retinal neovascularization; in fact, often some of these eyes never completely vascularize.

I'm wondering in these studies, with all the tools and imaging you have available, do you know what percentage of eyes at the end of the trial still remained incompletely vascularized; and if so, was there any guideline in that study protocol on what to do with those eyes?

DR. HIRSHBERG: Yes. Dr. Vitti?

DR. VITTI: Bob Vitti, Regeneron. By looking at individual eyes, two-thirds of the eyes in the BUTTERFLEYE study that were originally

treated with aflibercept had complete vascularization within a disc diameter of the ora serrata, and in the FIREFLEYE study we see that increase to 74 percent.

So somewhere between a third and a quarter of the patients, to answer your question, would not have completely vascularized, however, this is consistent with the rate seen in the RAINBOW study after a two-year follow-up. You see patients in the 0.2-milligram group, and about 62 percent of those eyes had complete vascularization; so again, about a third of those did not.

DR. LAI: If I could follow up?

DR. CHODOSH: Yes, please, go ahead.

DR. LAI: Was there a study protocol recommendation for those eyes?

DR. HIRSHBERG: Can we just ask Dr. Örge to address another component of the question?

DR. ÖRGE: Faruk Örge again. I just also want to remind that there is a FIREFLEYE and BUTTERFLEYE extension studies; that the babies continue to be followed, and the study does not

preclude the appropriate follow-up that is required per the provider. As you've mentioned, this is not an unknown phenomena, and a lot of babies, unfortunately, may have the PAR, peripheral avascular retina, that actually does persists.

But since these particular studies were finalized at 52 weeks, and as you know, new studies actually may say that if the babies don't really grow beyond a certain area, and by 65 it seems like they may not be progressing further, maybe a definitive treatment may be required. But this was beyond the scope of these particular studies.

DR. CHODOSH: Okay. This is Dr. Chodosh again. The next question comes from Dr. Todd Durham.

DR. DURHAM: Good morning. This is Todd Durham. My question has to do with the time of recurrence of ROP.

In your briefing document, you cite average times of recurrence of ROP, and the first question about this is how were those means calculated since not all study participants had recurrence of ROP?

And the second part of the question is, do you have any display, like a Kaplan-Meier curve or any other descriptive summary, that will show us the earliest and latest times of recurrence of ROP?

DR. HIRSHBERG: Thank you. Dr. Musser will address those questions.

DR. MUSSER: Hi. Good morning. This is Bret Musser with Regeneron biostats. Excellent question because we actually have the graph that you're requesting.

What will appear here are the Kaplan-Meier curves for time to the first recurrence of ROP, on the left for BUTTERFLEYE, on the right for FIREFLEYE. For those Kaplan-Meier curves, each decrement in the line that goes down represents the event that occurs, and if you see a blue dot or a red vertical line, that's the last observed followed for a particular baby in the study.

As you can see from the graph, most of these recurrences did occur within the first 16 weeks; they all occurred within the first 6 months, but if you look about by day 113 in both studies, that's

the limit of most recurrences in the trial

DR. HIRSHBERG: Thank you.

DR. DURHAM: Thank you.

DR. CHODOSH: Okay. This is Dr. Chodosh again. I believe Dr. Chiang had a question.

DR. CHIANG: Yes. Thanks. I have a few questions. One of them is recurrence in that previous graph you showed. How do you define recurrence? Does that mean reactivation of any disease or does it mean occurrence of what you called active ROP, meaning treatment requiring reactivation?

My second question is similar to Dr. Joniak-Grant's. I apologize if it was the same question, but it was that there was a protocol saying that there could be up to 3 injections per eye, and I just wondered what the basis for that recommendation was. And my third question deals with deaths. Obviously, it was a little bit striking that there were deaths only in the aflibercept groups in both of these studies, and I know that Dr. Green's data showed that these were

sick babies who died.

But my specific question is, the randomization data I believe implies that the two groups were pretty similar when they started, so I was just wondering if you feel that this was some sort of statistical aberration, or if the groups truly weren't equal when they started, or if you just have some -- if you could speak a little bit more to that. Thank you.

DR. HIRSHBERG: Dr. Vitti will address the first question, and then Dr. Suzanne Green will address the second part of your question.

DR. VITTI: Bob Vitti, Regeneron. Recurrence was cataloged not based on recurring to type 1 but rather any recurrence that was seen in terms of investigator's assessment of active ROP.

DR. CHIANG: Well, active ROP as defined in the study meant it needed to be treated, which is not what I just heard from you. So I just want to make sure that I understand what it meant to recur. Did it mean that any disease came back or did it mean that treatment requiring disease or active

ROP, as defined in these studies, came back?

DR. VITTI: It meant that any treatment -- I'm sorry, any recurrence. So I misspoke; not active ROP as defined in the protocol, but rather any recurrence irrespective of whether treatment was required.

DR. CHIANG: Got it. Thanks.

DR. CHODOSH: Okay. This is Dr. Chodosh. We have about 6 minutes left before the next scheduled change, and we're going to go up until that time, and then we will move the remaining questions until after the lunch hour, where it looks like we'll have time.

Dr. Joniak-Grant, please go ahead.

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. Following up on Dr. Chiang's question, what percentage of recurrences required treatment? That would be my first question, and then I do have a couple more.

DR. HIRSHBERG: Dr. Vitti?

DR. VITTI: In the BUTTERFLEYE study, 37 patients recurred that were randomized to

aflibercept. Requiring treatment, can I have the other slide that shows -- as you can see in this slide here, patients with type 1 ROP, 33 percent of patients in the BUTTERFLEYE study on aflibercept recurred to type 1 and 20 percent in the FIREFLEYE study recurred to type 1.

DR. ÖRGE: And does type 1 require treatment?

DR. VITTI: Correct.

DR. JONIAK-GRANT: Okay. Then my other question is, when in your view is follow-up complete? Can you speak to any of that, or not at this time?

DR. HIRSHBERG: Dr. Örge will address this question.

DR. ÖRGE: Faruk Örge, ophthalmology. I think a person who is dealing with ROP, and I can speak on behalf of the company's guidelines as well, that they're very much lenient with the AAP guidelines, that the follow-up needs to continue until the ROP is either finalized, meaning the disease process has ended either with a treatment

or naturally that the vessels have fully grown, and it needs to continue until that point, and that needs to be in the labeling as well.

DR. JONIAK-GRANT: Thank you.

DR. CHODOSH: Okay.

Dr. Murray, we can either do your question now if it's short or after lunch break, based on our schedule. If you can ask it quickly, we'll try to address it. If it's not fully answered, we can come back to it. Go ahead.

(No response.)

DR. CHODOSH: Dr. Murray?

(No response.)

DR. CHODOSH: Okay. Maybe Dr. Murray is on mute, I'm not sure. But I think since it's 11:13, and if Dr. Chambers is prepared, we will now proceed with his presentation, the FDA presentation by Dr. Wiley Chambers. Thank you.

FDA Presentation - Wiley Chambers

DR. CHAMBERS: Thank you very much, Dr. Chodosh, and if I can have my slides.

Thank you. My name is Wiley Chambers. I am

the director of the Division of Ophthalmology, and I will be making the FDA's presentation. The mission of the Center for Drug Evaluation and Research, which is what I am part of, is to ensure that safe and effective drugs are available to improve the health of people in the United States.

We clearly recognize, with there being no pharmacological treatments for ROP, that there was an unmet medical need. At our disposal, we have some different methodologies and some different both stick and carrot ways to encourage trials and ways to require trials, at least for pediatric trials.

In most cases, we are purely reactive. We react to trials that are submitted to the FDA. We approve products when applications have been submitted to us. We don't usually have the opportunity to ask for further information, but in pediatrics we do. So for some applications, we can impose potential requirements, and that's based on what's called the Pediatric Research Equity Act or PREA; in other cases, we can offer incentives by

asking for studies, based on the Best Pharmaceuticals for Children's Act, also known as BPCA.

In this particular case, asking for or having required studies, there needs to be an application submitted which has a pediatric component to the indication that's been requested, and the goal is to try and basically expand the labeling for that product. The incentives, which are part of the BPCA, provide an opportunity for the FDA to ask for specific studies, whether or not that indication was previously submitted, and to potentially provide exclusivity to sponsors who voluntarily complete studies under the written request.

In this particular case, the requirement section was not an option. EYLEA's indications -- neovascular AMD, retinal vein occlusions, diabetic macular edema, diabetic retinopathy -- do not have pediatric patients, so it was not possible to ask for studies in these particular indications for pediatrics because those

diseases do not occur in pediatric patients.

In addition, for the treatment of retinopathy of prematurity, while we might have the opportunity to ask for additional studies, the treatment of retinopathy of prematurity was granted orphan designation based on the number of patients in the United States that have retinopathy prematurity, and because the product received orphan designation, they are exempt from any of those requirements.

The option the FDA did have was to write a written request, and so based on Section 505A of the federal Food, Drug, and Cosmetic Act, and pursuant to Section 351(m) of the Public Health Service Act, the FDA made a formal written request to obtain pediatric information on aflibercept. The written request was issued June 4, 2019, and it specifically said we were requesting information on aflibercept and that studies be done to look at aflibercept's potential use in the treatment of ROP.

We requested two studies. The primary

objective of the studies was to evaluate the efficacy, safety, and tolerability of intravitreal aflibercept in patients with ROP, and we required that the protocols and statistical analysis plans had to be submitted and agreed upon by the division. This is sometimes a challenge when we're going into new areas.

In this particular case, the length of time that the study needed to go on for, or should be required, was a source of debate. You've heard through the studies that have been presented so far how the time may get extended, and so instead of something that is 12 weeks/24 weeks, when you may be dealing with the first signs of seeing ROP, we knew we wanted a time that went farther on to allow potential repeated treatments if necessary, but still a time that was doable for these indications.

So for study 1, we asked for a randomized, parallel group, controlled study of at least 52 weeks in duration. We knew that developmentally, the only time to get better systemic evaluations of the potential effects of

aflibercept systemically, and/or what visual acuities might ultimately be obtained, was to ask for time that extended into basically year 5. So we asked for follow-up of a 5-year timepoint so that we can ultimately determine whether there are potential systemic effects that contribute to developmental concerns when the children are 5 years old. We also knew that retinal photography was becoming more and more used within these trials, so we asked that the trials include an assessment of retinal photography.

Recognizing that a 5-year follow-up is a relatively longer period of time, we asked for a commitment that they be included, but it was not necessary for the terms of the written request as far as granting exclusivity. This has been a common practice when we have asked for long-term follow-up. Study 2 asked for essentially the same thing. We wanted not necessarily duplicate or exact replication, but we wanted two studies to see how robust the findings necessarily were.

The design in each case was permitted to be

either a superiority design or a non-inferiority design. We recognized that there had been, during the past, both treatment with cryo and treatment with laser, and recognize that those were potential modalities for which a non-inferiority design could be performed; but we also opened the possibility of demonstrating superiority, recognizing that some people believe that anti-VEGF treatment offered the opportunity for superiority.

Statistical plans had to be agreed upon by the division. They were in fact reviewed and agreed upon Demographic characteristics and adverse experiences all needed to be descriptively summarized and compared between both groups, and you've heard that was done.

The primary endpoint was decided to be the absence of active ROP, and you've heard some description about whether that is necessarily the best term, but at the time that we were designing the trial, that was thought to convey what we were looking for; and in addition, we wanted the absence of unfavorable structure outcomes at a 52-week

timepoint, and by that we meant things like retinal detachment but not limited to retinal detachment.

The written request also required, as does the law that allows us to write written requests, that labeling had to be submitted following the completion of those trials so that we could incorporate the findings from the studies into the labeling to better share that information.

As written within the law, regardless of whether the studies demonstrated the aflibercept injection was safe, pure, potent, or whether the studies were inconclusive, those study results needed to be included in the labeling. And you see an example that Regeneron has submitted proposed labeling, and the purpose of this meeting is very much to discuss what should be in that label.

Aflibercept is BLA 125387, and this is Supplement 75 that we're discussing. It was submitted August 11, 2022. The FDA under the user fee provisions has a 6-month time frame to review that, so we expect to make a decision by six months after August 11, 2022 or February 11, 2023. The

contents of the supplement consisted of FIREFLEYE and FIREFLEYE NEXT, BUTTERFLEYE and BUTTERFLEYE NEXT study report, and labeling.

To talk a little bit more about the rationale and why we agreed to a control arm, we consider laser treatment to be a viable alternative to anti-VEGF treatment. You've heard about some of the pros and cons about why one or the other is necessarily better, but we thought it was a legitimate comparison. Another potential comparison could have been cryo, but we think because laser treatment is more widely used and there are advantages in the minds of many people of laser treatment over cryo, that it was probably more reasonable to expect a laser treatment comparator.

We had some estimates from the RAINBOW study as far as efficacy, but obviously the RAINBOW study was a single trial. The amount of information you can get from any one single trial gives you estimates but not necessarily a definitive answer; so looking back at what we had available at the

time, we had some natural history information based on the multicenter trial of cryotherapy conducted back in the 1980s and published in 1990. That showed an actual history.

For patients that were randomized between cryo and no treatment, the natural history reported a fairly similar endpoint of about 55 percent success rate -- or failure rate. The cryotherapy at the time reported a 75 percent similar endpoint; from BUTTERFLEYE, you've heard reported 66 percent; for laser treatment and anti-VEGF, depending on whether you just look at zone I or look at zone II, a range of 80 to 88 percent since we didn't know exactly what the proportion was going to be of zone I versus zone II in these trials before the trials were run.

We set a relatively conservative non-inferiority margin. As Dr. Murray has referenced, there have been reports of relatively high efficacy, and we wanted any comparison, before we said that they were the same, to be very close, so we set this plus or minus 5 percent as being

what would be basically equivalent.

I won't go much into the primary endpoint because you've already heard it presented. Basically, each of the studies showed efficacy both in the aflibercept and the laser group of approximately 80 percent. The differences were within 2 percent, but because of the size of the study and variability, the confidence intervals are relatively wide.

You can argue that we should have preplanned this and should have made the studies larger. That would have been one way to avoid the large error rates around these differences. Part of the reason we thought we could get away with having the size studies that we did was there was an expectation that the anti-VEGF treatment would do a little bit better than the laser. That obviously did not occur, so ultimately both trials failed to meet the 5 percent non-inferiority margin, and therefore neither trial supported the prespecified hypothesis.

Potential reasons have already been

partially discussed. Some of it was likely because the trials were underpowered based on the three underpowered calculations that were done based on the information available at the time. The population mix between zone I and zone II appears to make a difference in what the efficacy rate is, and also it's been alluded having photographs to assure adequate laser treatment is likely to have increased the efficacy of the laser population, or the patients treated with laser. So we're left with the natural history that was expected to be about 55 percent, cryo therapy that was expected to be somewhat around 75 percent, and both aflibercept and laser in FIREFLEYE and BUTTERFLEYE around 80 percent.

Our goal was not necessarily to match what is laser therapy, but to know what aflibercept therapy would be so that we could inform clinicians and the parents of patients what to expect. The reason for doing a non-inferiority trial is usually because you do not believe you could have an untreated or natural history, and we continue to

believe it would have been unethical to not treat babies with some therapy that we thought was potentially effective.

The labeling that's been submitted includes changes to the indication; dosing and administration; adverse events section; pediatric use section; pharmacodynamics; pharmacokinetics; and clinical trials sections. These are all appropriate sections to potentially change, but we would like comments from the committee on both the proposed changes and any modifications they have, or any other labeling changes which they think would be appropriate to better inform the public on the findings of these trials and the potential best use of this product for retinopathy of prematurity.

The indication that was added was treatment of retinopathy of prematurity; this or some modifications we would like to consider. For dosing administration, as you've heard, the dose is different than what is given with aflibercept for the other adult indications. The agency has proposed some minor modifications to the labeling

that was proposed by Regeneron. As is the case for all of these labeling recommendations, this is a work in progress, and we very much are looking forward to comments from the committee on any potential changes, both from the original and from the modified.

We struck the limitation on giving the treatment within the first year because, in general, we've not seen any safety reasons why you couldn't give it at, say, week 53. That doesn't mean we are necessarily recommending treatments outer the longer periods of time. It's not just with laser treatment; it becomes more difficult to give individual injections as these infants get larger, but we thought one year was arbitrary to limit it.

The same thing with day 28; we thought day 28 was relatively arbitrary. We have for anti-VEGF therapies, from a timing perspective, thought that day 28 is not magic. We do think there needs to be some time so that the anti-VEGF systemic level is reduced before the next therapy,

but we are proposing day 25 as a limitation there.

EYLEA currently comes in both a glass-filled vial, as well as a prefilled syringe. Because the dosing amount is different, we believe that using the syringe may potentially lead to dosing errors, so we agree with Regeneron's suggestion stating that they should not use the prefilled syringe, but instead draw it up from the vial.

There is currently not stability information, to my knowledge, on a smaller prefilled syringe. We certainly are willing to entertain comments about whether that's good or not a good idea to go to a prefilled syringe with a smaller fill volume. We also think, in general, it's better to state what should be done as opposed to what should not be done.

To describe the dosing, there was also a section that was added in the dosing administration section. We do recognize that giving 0.01 milliliters, or 10 microliters, is a very small dose and frequently difficult to see in the size syringe that is being proposed and that was

used for the clinical trial; the clinical trials, plural.

The site of the injection is slightly different in the neonate, so that's described. Adverse reactions were relatively few, as seen within the 52-week period of time. Whether additional adverse events can be recognized during the further follow-up in 5 years remains to be seen. Because of this relatively small number, we don't think that tenths of percentages adds anything to those numbers; in fact, makes it probably more difficult to read, so we rounded those numbers.

Pediatric use is a specific section that describes pediatric use in the labeling of a product. We have proposed a modification for the pediatrics use section, describing what the rationale for using it is, i.e., that the clinical course expected from using an anti-VEGF would be better than the expected natural history in untreated subjects. Again, we would welcome any proposed changes to this.

Pharmacodynamics, we have not found to be useful. While it was measured in the ROP patients, we don't think it provides useful information to treating these neonates with retinopathy of prematurity, so we suggested that it get struck. Pharmacokinetics provides the actual numbers. We think it's probably more for academic purposes, but we have the numbers, so it's probably useful to provide them.

Immunogenicity was evaluated in these patients and found to be the same low level of immunogenicity, and we have yet to see any consequences either in the neonates or in the adults treated with aflibercept, so we've sought to state that, but minimize the importance since it hasn't been clinically relevant with the use of aflibercept.

The clinical studies section is supposed to get described so that clinicians understand what was done. This section has been significantly altered and, again, what you see in the next couple of slides is an agency proposal. We would welcome

comments on how this section should be written.

This next slide is just a further portion. Again, we tried to reduce some of the redundancy since both trials were essentially the same, with the exception of a couple different modifications, the 2 to 1 randomization versus the 3 to 1 randomization. Those differences in the number of patients in each group does make it a little difficult to sometime figure out what happens with rare events such as deaths because there were more patients exposed in aflibercept than there were with laser. So when you look at numbers such as deaths, you had significantly more patients exposed to aflibercept than the laser during the trials. This ratio is described in this paragraph.

The efficacy has been listed and described. We have not described any of the secondary endpoints, and we did not describe them because by the general issues that are involved with multiplicity -- meaning if you look at multiple different endpoints -- you have the opportunity, just by chance, of seeing findings. So we ask that

endpoints be prespecified as far as order to control for the multiplicity.

If you follow that type of statistical approach and you fail at any one point, you are not allowed to look at the next set of endpoints. So while there was originally a primary endpoint and secondary endpoint for this trial, once each of the two trials failed their primary endpoint, meaning they had not shown non-inferiority, by statistical rules you cannot look at the secondary endpoints, and so they are not currently described in the clinical trials section.

I'm happy to take any questions. Thank you very much for the opportunity to present.

Clarifying Questions to FDA

DR. CHODOSH: Thank you, Dr. Chambers.

This is Dr. Chodosh again. We will now take clarifying questions for the FDA specifically, and again, please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your question.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move to the next panel member.

It looks like our first question will come from Dr. Joniak-Grant. Please go ahead.

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. I have three questions. I'll just ask each in turn.

As a patient representative, I am not an ophthalmologist; so do VEGF and -- I'm not sure how you pronounce this -- PIGF -- and maybe you do -- which aflibercept binds to, are we aware of the roles that these supplements play in the development of any other structures outside of the eyes? That's my first question.

DR. CHAMBERS: This is Wiley Chambers. I do not know that I know the answer to that. PIGF is placental growth factor. I'll turn it over to see if Regeneron has an answer, but I do not know the answer.

DR. HIRSHBERG: This is the sponsor here. Dr. DiCioccio will address the question.

DR. DiCIOCCIO: Yes. Hi. Tom DiCioccio. Outside of the indication, we are also not aware of any known implications of inhibiting PIGF. It does seem to have some minor role possibly in ophthalmology, but I'm not aware of anything else either, as is Dr. Chambers.

DR. CHODOSH: Dr. Joniak --

DR. JONIAK-GRANT: I'm talking about the VEGF.

(Crosstalk.)

DR. JONIAK-GRANT: Sorry. What about the VEGF?

DR. CHAMBERS: This is Wiley Chambers. There are clear potential implications. VEGF is not limited to the eye. The body uses VEGF as a

marker of tissue to grow new blood vessels where it believes it's necessary. The exact level of anti-VEGF that occurs, that basically systemically is available that would inhibit the body from its necessary functions, to my knowledge is not known. So while it's possible to measure it, we know there is some. We do not know what level would stop any additional growth of tissues systemically within the body.

DR. JONIAK-GRANT: Thank you.

Then my second question is do you believe that the laser comparison groups -- seeing that we've had some unexpected results in efficacy with it being the comparison group sizes of 27 and 38 -- are large enough to make reasonable comparisons? A lot of the things with adverse events and such, we're always comparing these two groups. In FDA's estimation, are these sample sizes large enough, despite the large confidence intervals?

DR. CHAMBERS: So more is always better, but we are faced with a balancing act of how long do

you study a particular product and how many patients do you expose, because during the study development period, you are not necessarily labeling a product for that use, and that has implications.

So the numbers that were arrived at were based on the hypotheses prior to the trials being done. It's always better to have the results in hand and know what was going on, but we didn't have that at the time we planned the trial. We think this was a reasonable estimation to give an idea of what was going on with anti-VEGF therapy, and aflibercept in particular, so we thought it was a reasonable number to be able to make an assessment about whether the product should be approved or not.

DR. JONIAK-GRANT: Okay. Then my last question, is there any concern with the lack of black or African-American participants? I'm thinking, for example, there's more risk of sickle cell, and that can cause clotting issues. It was mostly a white and Asian population, but would

including individuals of other races impact adverse event outcomes?

DR. CHAMBERS: The trials did enroll -- I mean, there were no restrictions on who was able to be enrolled. It did enroll multiple different races. I don't know that the -- the population that was studied is probably a little bit higher in the Asian than would be expected in the U.S. population, but otherwise is relatively comparable to what you would expect in the U.S. population.

The impact on sickle cell, I do not know what the implications are. The ability to have included enough patients with sickle cell in this rare population I think would be extremely difficult to find, but obviously it would be nice to know the answer, and to my knowledge, we don't have that.

DR. JONIAK-GRANT: Okay. Thank you for the information.

DR. CHODOSH: Great. Thank you.

I believe Dr. Michael Chiang is next with a question.

DR. CHIANG: Jim, thanks.

I have two questions. One of them is if you could clarify what the basis was for saying that we can inject up to 3 times per eye. My second question is that I think in a lot of these slides we present, you've got option A, which is aflibercept, and then option B, which is is laser. And in the real world, I think what happens is, as it's been alluded to, many of these babies get aflibercept followed by laser.

One of the challenges is that there's not universal consensus on when to laser after aflibercept , and then what the criteria are for laser. I see more and more people doing laser after almost every anti-VEGF injection because so many of these babies don't fully vascularize or develop reactivation of disease.

So my question is with the aflibercept versus laser question. I hear one question from parents all the time, which is, "If you're going to treat with anti-VEGF and then follow with laser, why not just do the laser?" I just think that

that's something -- so my question would be if there's a way that that can be just clarified for patients up front in the labeling?

DR. CHAMBERS: This is Wiley Chambers. To answer your first question, the choice of three was arbitrary. The goal of the trials that the agency asked for, we're just trying to get an understanding of aflibercept. As I'm sure everyone on this call knows, a single trial, or even two trials, do not answer all the questions that people might have about the safe and effective use of a particular product, and certainly not all the different situations.

The FDA's goal was to try and determine whether there was a safe and effective way to go and use aflibercept in the treatment of retinopathy prematurity. It was not to necessarily come up with all of the different ways that it could be used. I certainly encourage additional trials being done in this area, and specifically I would have no objection to the National Eye Institute funding additional trials to look at some of those

questions.

DR. CHIANG: Thanks, Wylie.

DR. CHODOSH: Okay. I'm looking for more questions.

Dr. Murray, do you have a question for the FDA?

(No response.)

DR. CHODOSH: I believe you may be on mute.

DR. CHAMBERS: Tim, you're on mute.

DR. CHODOSH: Dr. Murray, you are on mute. If you have a question for FDA, can you please [inaudible - feedback].

DR. MURRAY: Can you hear me?

DR. CHODOSH: We can hear you now. Thank you.

DR. MURRAY: Okay. My phone says I'm not on mute.

My question is for Dr. Chambers. We have two clinical trials, neither of which meets the primary endpoint of the trial, yet we're discussing indications and potential usage. And I just wondered what the thought process is when a primary

endpoint is not met in two clinical trials for a change in labeling. Thank you.

DR. CHAMBERS: This is Wiley Chambers. Two things happened here. One is the question about whether the product really is safe and efficacious, and the trial endpoint was based on our feeling that it would be unethical to have included a no-treatment arm, but the reason for having the control is to get a better estimate of -- well, in this particular case, we did a non-inferiority because we couldn't include a no-treatment arm.

So the question that we really want to know is whether the product is safe and efficacious. And we believe that the difference between what the natural history would be for this particular product -- well, what the treatment arm demonstrated versus what the natural history would have been, demonstrates efficacy for this particular product. But the second point to this is we are required by law, when we write a written request, to include information about that trial in the label, whether or not the trial was successful.

DR. MURRAY: Thank you; very helpful.

DR. CHODOSH: Thank you.

So Wiley, if I might, as I understand it, there are enough concerns about the particulars of laser therapy, and in context, it would be unethical to do a no-treatment arm, and that's why you've sort of come to the place you are now? Does that express it?

DR. CHAMBERS: Yes. No, it is really both. It is, one, we're required to put it, so we're going to have to write something in the label that talks about using it; and, two, we do know what the natural history would be. The natural history is not a good outcome. So to the extent that we believe this is better than the natural history, we think it's worth identifying that it is better than the natural history in the labeling.

DR. CHODOSH: Thank you, Dr. Chambers.

We have another question from Dr. Joniak-Grant. Please go ahead.

DR. JONIAK-GRANT: I'm sorry. I forgot to put my hand down.

DR. CHODOSH: Okay. Alright. That's fine.

DR. JONIAK-GRANT: No question.

DR. CHODOSH: This is Dr. Chodosh. Hang on a minute. We're a bit early, and I'm trying to get some instructions on whether we should break now or go back to Regeneron. Dr. Murray has a question, and --

DR. CHAMBERS: We've --

DR. CHODOSH: I'm sorry. Say again.

DR. CHAMBERS: There's another hand up.

DR. CHODOSH: Dr. Atillasoy has put his hand up. Please go ahead.

(No response.)

DR. CHODOSH: You're muted. There you go.

(No response.)

DR. CHAMBERS: No, still muted.

DR. CHODOSH: Dr. Atillasoy, did you have a question? Your hand went down, but you're still muted.

(No response.)

DR. CHODOSH: Okay. If everybody would just hang on for one minute.

(Pause.)

Clarifying Questions to Applicant (continued)

DR. CHODOSH: Dr. Murray, are you still there? And if so, would you like to ask your question for the sponsor?

DR. MURRAY: I am still here. Thank you. Tim Murray, Miami.

I wanted to go back to the slides with the 40 percent recurrence rate from the use of aflibercept and ask for a little bit of clarification for that. It seems that the recurrence rate of disease was significantly different over time between laser and aflibercept, and I wondered if that registers a concern.

DR. HIRSHBERG: Let me ask Dr. Vitti to address the first question about the data, and then Dr. Örge to provide his clinical assessment.

DR. VITTI: This is Bob Vitti, Regeneron. Let's look at the rates again; 40 percent recurrence rate in the BUTTERFLEYE study for aflibercept and 31 percent in FIREFLEYE.

I'm not a hundred percent sure of your

question when you asked about over time. What did you mean by that?

DR. MURRAY: Yes. The other data point was a Kaplan-Meier analysis looking at time to failure and then overall failure. This chart also is helpful. It does suggest a significant recurrence of ROP within the first 52 weeks, and I think that reiterates Dr. Chiang's concern when he mentioned that many children now are being treated with an anti-VEGF followed by a consolidating laser, and that is a key point that often the parents will ask why not laser up front?

I'm just interested in what the thoughts are for this recurrence rate. It, for me, was higher than expected with an anti-VEGF treatment, and again reiterates my concern that the dosing structure for aflibercept may be too low for this unique population. Thank you.

DR. HIRSHBERG: Dr. Örge will address your question.

DR. ÖRGE: Faruk Örge from ophthalmology. Coming to the practical points on different

treatments, first of all, we had discussed the laser treatment at a very early stage, meaning when the baby is younger, when we apply the treatment, as we initially have seen in the disease process, it requires the entire avascular area to be lasered.

Now with the anti-VEGF treatment that is applied to the patient -- and I'm going to show you this slide again -- again, coming back to this example that I had given, when we apply the anti-VEGF, it appears to not only regress the disease or the abnormal vessels to go away, but allows the normal vasculature to continue to grow.

At least in the immediate action where we tend to see the babies to be still fairly vulnerable systemically in the NICU, who are more susceptible for anesthesia and sedation and somewhat difficult to transfer, even to a different room, these effects, if you allow the abnormal vessels to go away and allow the normal vessels to grow, then we will have a difference on how much laser needs to be applied, even if you need the

laser.

Now, when we look at our study, a good portion of the babies who just received treatment is all they needed, at least at the 52-week mark, which some of them actually came to the point that they did not need laser at all. So the vasculature had matured enough that it came to the 1-disc diameter that we tend to see. So doing an injection has these advantages for the long run, but acknowledging that a certain amount of a group still will need the vasculature to be followed until they either come to this or we know they will not be progressing, then maybe the follow-up laser needs to be done.

As we were discussing priorly, I think that is going to be an ongoing discussion. We're still learning quite a bit about what is the appropriate treatment. Do you do laser initially, anti-VEGF, or in combination? When do you apply the laser treatment? I think it's pretty much in a flux at this point in the community and the comfort level, but what we know is, again, the anti-VEGF allows us

to at least buy more time to apply less laser and have less complications due to that. Not only that; if we apply the laser, it tends to be more in an outpatient basis or in a little bit more stable condition when the babies are older so the systemic problems somewhat have subsided.

I think beyond all, when we look at the community, the dosage of the anti-VEGF and which anti-VEGF to use is so variable, and having an approved product really allows us to really study for this amount, or for this dosage, on what needs to be done a little more appropriately. So I think for the overall discussion, while we're learning, having that kind of a stability on what needs to be done as a community is extremely helpful for us to really understand what needs to be done laser, and when. Thank you.

DR. CHODOSH: Dr. Murray, did you have any follow-up?

DR. MURRAY: I'm good with that. Thank you, Dr. Chodosh.

DR. CHODOSH: Thank you so much.

Are there any other questions? I don't see any other hands up.

Not seeing those, we are going to right now break for lunch. This is a little bit earlier than planned, and instead of 1:45, we're going to reconvene at 1:15 p.m. Eastern time. Please, everybody take note, 1:15, not at 1:45 what's in your schedule.

Panel members, please remember there should be no chatting or discussion of the topics with other panel members during this lunch break. Additionally, unlike what you may have been told, since we're starting lunch early and finishing lunch early, please rejoin at 1 p.m. to the network to be sure that you're connected before we reconvene at 1:15 p.m. Thank you very much, and we'll see you all after the break.

(Whereupon, at 12:04 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

Open Public Hearing

DR. CHODOSH: Hi, everybody. This is Dr. James Chodosh rejoining after lunch. We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it's important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in this

meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when you are recognized by the chairperson, myself. Thank you very much for your cooperation.

Speaker number 1, your audio should be shortly connected. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record. Thank you.

MS. PRATT: Good afternoon. My name is Nicole Pratt. I have no conflicts or interests. I am not receiving any financial compensation. I'm here only because I want to share my experience with my son, Jordan Pratt, an ROP.

Jordan was born premature on July 13, 2000, weighing 2 pounds 4 ounces. He had a grade 4 brain bleed. The doctor explained to me that Jordan could develop developmental disabilities, vision loss, and other medical issues. Jordan was in the NICU for about 2 months. About 2 days prior to being discharged, they did a vision screening. That's when they saw that he was at risk of retinal detachment. I was informed that he needed to see a specialist, including an eye doctor. I got referred to a pediatric eye doctor, first, to get a comprehensive eye exam, then was referred to a

pediatric vision specialist who specialize in ROP. The specialist confirmed the diagnosis of ROP stage 3, and informed me that treatment wasn't recommended at that point; just to watch and wait.

We had to go back every 2 weeks for about 3 months. I also enrolled Jordan in the Early Intervention Vision Therapy program where I lived, which he continued until he was about 3 years old. It was a lot to handle, and this was more than 20 years ago, and I didn't have a lot of information. I was and am a single working mom with a child with many sorts of medical needs and not a lot of options, especially if Jordan's condition had changed.

We went to the ROP specialist, a vision therapist/retinal therapist eye doctor. Jordan had early intervention services until three, as I mentioned, and that was key, and that's what helped him to do very well with his vision. The only thing, while he was young, the sunlight would bother his eyes so that he would have to wear hats. When he turned 21, he started having headaches, and

in addition he also has mild cerebral palsy. I took him to the eye doctor, and he was diagnosed with nearsightedness, which he now wears glasses for.

I am very pleased here to share our story. Thankfully, Jordan's ROP didn't require treatment like the one you're considering today, but having additional options supported by clinical data, which is clear information for parents, could be and is vitally important. I also would like to say I was pleased when I saw your discussion questions. Communicating the information about this treatment is such an important part of making it available to families. I'd like to also ask that you make sure pediatricians especially have the information as much as possible so that they can give parents information and help parents/families make informed decisions for their children.

I faced multiple diagnoses over the last 20 some odd years with him. I would have loved more information and more options for Jordan's ROP if he had needed it. Based on what you all are

doing today, parents in the near future may have additional options for ROP, as well as the information to understand the pros and cons of different treatments and the possible outcomes. Safety is the importance of their kids and families.

Thank you for your time and listening to Jordan's experience, and listening to my thoughts, and as a mom who went through this many years ago about how important what we're discussing today gives patients and families some diagnoses [indiscernible]. Thank you.

DR. CHODOSH: Thank you so much for your comments.

Speaker number 2, your audio should be connected now. Will you begin and introduce yourself, stating your name and any organization you're representing for the record? Thank you.

DR. DUNBAR: Hello. My name is Jennifer Dunbar, and I'm a pediatric ophthalmologist. My financial disclosures include, in the past, I've participated as a subinvestigator in the RAINBOW

clinical trial for a VEGF inhibitor for ROP and was paid for this, and I have also participated as a site principal investigator in the BUTTERFLEYE trial for EYLEA, and I was paid for this. I'm not compensated for presenting today, however.

I completed my pediatric ophthalmology fellowship in 1996, and since that time, I have cared for infants with retinopathy of prematurity in the tertiary care setting. Since 2002, I've practiced at Loma Linda University in California, who's neonatal intensive care is licensed for 86 beds. I often see 20 inpatient babies each week, many of them with gestational age in the 23- to 24-week range. In addition, I see these patients in the years to follow for their outpatient follow-up.

Because of my 20 years experience at one institution, I have a unique perspective on the long-term suffering of individuals with severe ROP. While a clinical trial may last around a year, laser may have effects which last a lifetime. This highlights the need for VEGF inhibitors such as

EYLEA to receive FDA approval for the ROP indication. To illustrate this, I would like to share the stories of three patients who I have known since infancy.

The first patient is an 11-year-old female who received laser in both eyes as an infant for very severe ROP. Although her ROP resolved, after laser and in infancy she experienced ocular ischemia syndrome in her left eye, which led to a serious retinal detachment in that eye, and her vision is currently counting fingers in that left eye.

About one month ago, she experienced herpes-related anterior uveitis, which followed herpes keratitis. This was also complicated by glaucoma and threatened vision in her only seeing right eye. This illustrates that these patients are not immune to others severe eye problems unrelated to ROP happening later in life, and that every little bit of vision that we can save can help protect them.

The second patient is a 19-year-old female

who received laser as an infant in both eyes. This has been complicated by cataracts and glaucoma. Her remaining vision is 20/200 in her better right eye and hand motions in the left eye. In addition, she has experienced two late retinal detachments in the left eye at ages 10 and 15 years, both requiring surgery.

Finally, the third patient is a 13-year-old female who had the worst ROP I have ever seen. In addition to severe ROP in the back of the eye, in the retina she had very severe iris-plus disease with engorged vessels in the tunica vasculosa lentis, which surrounds the lens in premature infants. When I attempted laser, these vessels broke and bled. They took away view of the retina and they prevented any further laser, and they prevented complete treatment of the ROP.

We were able to use VEGF inhibitor to be injected under compassionate use. This was the first time I saw VEGF inhibitor injected off label to help control the ROP. It calmed the ROP down enough to enable laser to be performed later in

this very difficult case. At the present time, I still see this patient, and her vision is 20/40. She's able to participate in regular school and to walk around.

In summary, ROP remains a significant challenge to this day. Laser for severe ROP has the potential for late side effects, which are not reflected in the time frame of clinical trials. Children deserve their ophthalmologist to have a full armamentarium of tools, including FDA-approved VEGF inhibitors like EYLEA to fight this blinding disease. Thank you so much for your time.

DR. CHODOSH: Thank you, Dr. Dunbar.

Speaker number 3, your audio should be connected now. Please begin and introduce yourself by stating your name and any organization you're representing for the record. Thank you.

DR. CHAN: Hi. Thank you, Dr. Chodosh. My name is Paul Chan. I'm the professor and department head of ophthalmology at the University of Illinois at Chicago. I'm also the director of the pediatric retinopathy service.

Let's go to the next slide. I'm currently here presenting as a member of the board of directors of Prevent Blindness. For disclosures, I participated in the BUTTERFLEYE study and had potential patients who were part of the study, but none were selected for enrollment. I'm also an advisor and a consultant for Genentech, and an owner of Siloam Vision, which deals with ROP care.

What I want to go through today, as the previous speaker had mentioned, is the discussion around treatment options for ROP and why it's so critically important that we have these options. When we go through the evolution of treatment and how treatment has evolved for ROP, we first started with peripheral ablation with fusion treatment, and then with laser, and then subsequently with bevacizumab.

I think when we have these discussions of why do we need treatment options, well, even with laser, especially in the most aggressive forms of retinopathy prematurity, there is a significant fill rate, and many children are very difficult to

treat. So now we are fortunate to have options such as anti-VEGF in the form of aflibercept and other medications to treat these children, and now we have data. With the BUTTERFLEYE and the FIREFLEYE studies, we're starting to see data, and most recently, data from the FIREFLEYE study was published, most recently, in 2022 with the international group, showing non-inferiority to laser using aflibercept 0.4 milligrams.

I just want to provide an example of a case that benefited from anti-VEGF, and here you can see these pictures, and I'm sure many on the call and many on the panel know this very well. You can have increased VEGF, which will produce new vessels in front of the eye, and you can see here in this picture those lines going radially into the center of the pupil, which will make it difficult to also perform laser.

As we look at the findings here, and as we all know right now, retinopathy prematurity is a disease that most commonly occurs in both eyes, so if a child is not treated appropriately or if

treatment fails, then that baby can be blind bilaterally. We can see here the plus disease in the vessels, in the vessels of the periphery and hemorrhage. This is posterior disease, and this is a patient that would benefit from anti-VEGF therapy.

This baby was treated with anti-VEGF, and what you'll see here is that instead of ablating and destroying the peripheral retina, you're allowing the vessels to grow more peripherally, improving outcomes potential. As a comparison, in this picture this patient had laser, and you can see here the destructive nature of laser treatment and how this might affect vision in the long term, and as previously presented, patients may develop significant myopia through life.

When we talk about retinopathy prematurity, it's a condition that will affect children. It is lifelong and can be devastating in terms of the visual disability and also lifelong morbidity. I think that right now we have options. We have options regarding treatment with laser and also

with anti-VEGF injections, and I think it's critical for physicians and families to have guidance on the safe use of intravitreal anti-VEGF injections, as we're starting to see more data come through.

In addition, it's incredibly important to educate families to empower them to make informed decisions for their children, and I think this is really one of the most critical points that we discuss. So now that we have the options, such as laser and these other intravitreal agents, we have to make sure that parents are aware that these are possibilities to treat their children. In general, having treatment options will not only save vision, but it will also save the lives of these children. As we know, many children who can't see will have more mortality than children who can, and it's important to save them that risk of developing blindness or ROP.

So again, I want to thank the committee and the panel for having me speak to you today and to discuss these treatment options for retinopathy

prematurity. Thank you.

DR. CHODOSH: Thank you, Dr. Chan.

Speaker number 4, your audio is now connected. Will you begin and introduce yourself, while stating your name and any organization you are representing for the record?

MS. CUNDIFF: Good afternoon, and thank you for allowing me to speak today. My name is Kathy Cundiff, and I have no financial interest in the outcome of this meeting, and I'm not being compensated for my time to share my family story. I do have a slide if you're able to pull it up.

I wanted to share stories of our family's experience with ROP after our triplets, Layla, Cameron, and Matthew, were born emergently at 24-weeks gestation in October of 2016. We were told early on that our children had ROP, and they would be closely monitored through their NICU stay and thereafter.

As a parent, eye exams and also head ultrasound testing days were the most gut-wrenching days for me. I would wait outside the room for our

retina specialist to tell me how much more advanced their ROP disease had progressed. I vividly remember one evening where I was alone in the hallway waiting for the retina specialist to give me an update after their exams, and he said, "All three of your children will very likely go blind." Cameron, Layla, and Matthew all had stage 3 plus ROP.

I immediately fell to the floor in tears. After I composed myself, I was told there was a couple of treatment options that may help stop the progression of their disease. Both laser surgery and an off-label injection were discussed. We spoke about the pros and cons of both treatments, including that the injection was not an FDA-approved treatment for ROP, and that there could be side effects along with the risk of peripheral vision loss with laser surgery. In that moment, I had to decide what to do, and together we decided the injections were the best option for our babies due to their advanced disease. I felt I had no choice but to say yes due to how bad their eyes

had gotten and the urgent need for treatment. I then had to sign off on medical waivers for all three of my babies for a treatment that I was fearful of and had not been proven for premature babies.

In December of that year when the triplets were 8 weeks old, we were told our son Matthew's ROP was on the verge of retinal detachment, and the best chance for him was to be transferred to a university level NICU where there was a retina specialist with more expertise for a second opinion on treatment. Again, we felt like we had no choice that day but to separate our family and transfer our son an hour away to give him the best chance at saving his eyes.

We spent the holidays that year between two hospitals while Matthew had laser surgery on both eyes. For that transfer for Matthew, we received a $15,000 ambulance bill that we could not pay at the time. We ignored the bill and focused on our babies hopefully coming home one day. Sadly, Matthew passed away at 4 months old after fighting

for his life. His severe brain injuries were worsening and his small body could not handle any more trauma. We buried our son, and then the following day brought Layla home, and shortly thereafter Cameron joined us. Both babies were on oxygen, and Layla with a G-tube.

The first 6 months of Cameron and Layla being home, we either had weekly or bi-weekly retina appointments with our local physician. I would transfer them to their portable oxygen tanks and had my camping chair in tow. You're probably wondering why a mom would bring a camping chair to a doctor appointment. You see, the local retina doctor who treated our babies, who is one of the only retina specialists for babies in the area, was so busy, his waiting room would be overflowing, but Cameron and Layla could not be around all those people due to their weak immune systems, so I would sit in the hallway in my camping chair, double stroller, and oxygen tanks in tow, while we waited 2 hours each visit to see the doctor after dilation.

Both Cameron and Layla received more injections after some of those visits, off-label injections, where again I had to make a quick decision and sign those waivers. I would walk away pale as a ghost wondering if I made the right decision for my babies. Throughout that first year, I was also harassed by creditors for Matthew's $15,000 ambulance transfer for his second opinion for his eyes. We had to dig into our savings to pay for the negotiated payment for our son who is no longer alive. As you can imagine, this was both mentally and financially draining.

Eventually, Layla also had laser surgery on both eyes. The first year of their life, we were fighting for their eyesight, among many other battles, and multiple hours of therapy each week. The micro preemie journey is one that is absolutely gut-wrenching, heartbreaking, and life-altering. The decisions we as parents had to make were absolutely awful and things no parent should ever have to endure.

I will say that after all our children went

through, their battle to save their eyesight was one of the most difficult. We have transferred their care to that university retina physician whom we still see every 6 months. If there is an FDA-approved treatment to give our babies a better chance at seeing the world, I urge you to please help babies like Cameron and Layla and Matthew, and families like ours. Thank you very much for allowing me to share our story.

DR. CHODOSH: Thank you so much for sharing your comments with us.

Speaker number 5, your audio is now connected. Please begin and introduce yourself by stating your name and any organization you're representing for the record.

DR. CLELAND: Hi. Good afternoon, and thank you for allowing me to speak. My name is Tim Cleland, and I am a retina specialist in private practice here, based in San Antonio, Texas. I'm speaking on my own behalf, and what follows is my own perspective. It is based on my experiences and interactions with other retina specialists,

neonatologists, and parents of premature infants. By way of financial conflict, I was an investigator in the BUTTERFLEYE study.

By way of background information, I have a bachelor's degree in electrical engineering and a master's degree in biomedical engineering from the University of Texas at Austin, and medical school and ophthalmology residency training while also here in Texas. I completed a fellowship in intravitreal retinal surgery prior to entering private practice.

I have been involved in the screening and treatment of retinopathy of prematurity for more than 25 years. I have also been in the ROP research arena for longer than that. Our group was involved in the CRYO-ROP study, ETROP study, the RAINBOW study, and the BUTTERFLEYE study. Our group currently provides ROP coverage and inpatient pediatric retina consultation services for the major San Antonio children's hospitals.

I personally cover the Methodist Children's Hospital neonatal intensive care unit, which is

110-bed, level 4 NICU. On average, I examine 30 premature infants per week in the NICU, as well as in the clinic. Over just the past 12 weeks, I have performed laser surgery on 6 eyes of 3 babies, and I've injected 8 eyes of four more premature babies. The smallest of these four is a baby born at 22 weeks gestation, with a birth weight of over just 1 pound. I'm happy to say he's doing very well.

Currently for treatment-indicated ROP, we know the gold standard is laser. Now, the indications for laser treatment are well described, however, there are times when a baby needs treatment but is too medically unstable for laser. There are other times when the retina is so immature, it makes sense to inject and anti-VEGF agent and then allow the retina to grow and apply what turns out to be much less laser at a later date. The other times, a baby has had laser but the disease remains active, and what to do?

Laser surgery for me involves a trip to the operating room and 90 minutes of general

anesthesia, typically. It happens occasionally that the pediatric anesthesiologist wants the baby to remain on the ventilator after the laser surgery is completed, and sometimes they do for days; sometimes longer. This is a proper and correct treatment for most babies, and we do it. The complication rate is low; success rate is high.

Intravitreal anti-VEGF injections on the other hand can be done easily and quickly at the bedside, usually with sedation and a topical anesthetic; but, as we all know, there currently are no FDA-approved anti-VEGF medications for ROP. We all do it off label because it works and because there are many papers in the literature that support its use, and as I have previously mentioned, sometimes we don't have any other option.

It can be a very difficult conversation with the parents of this fragile patient population; for example, on telling them their baby's ROP has progressed to the point where we need to treat, yet the attending neonatologist says general anesthesia

is too risky. So I tell them we're going to inject this medicine that works very well into their baby's eyes. Of course, I'm also obligated to tell them that the medicine I'm going to inject is not FDA approved for this indication, and currently there is no other medicine that is. Most parents respond with, "You're the expert; do what is best." Some respond with, "So you're telling me you're going to perform an experimental procedure on my baby?"

We need the FDA to support what we already do, specifically to approve a drug for treatment-warranted ROP. We as practicing retina specialists need an FDA-approved anti-VEGF medication. As I see it, our intent is not to replace laser with anti-medications; we need an FDA-approved drug that we can use along with laser to best treat these premature infants. Thank you for your time.

Clarifying Questions (continued)

DR. CHODOSH: Thank you, Dr. Cleland.

This is Dr. Chodosh again. This concludes

the open public hearing portion of this meeting, and we will no longer take further comments from the audience.

We will now entertain remaining clarifying questions. Please use the raise-hand icon to indicate that you have a question, and remember to put your hand down after you've asked your question. Please remember to state your name for the record before you speak and direct your question, if possible, to a specific presenter. If you wish for a specific slide to be displayed, let us know the slide number, if possible.

As a reminder, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move to the next panel member.

Now, I do believe that Dr. Joniak-Grant had asked a question of the sponsor that they needed further information or further time to gather that information, and we could go back to that question now if the sponsor is available and ready to

respond.

DR. HIRSHBERG: Yes, we are. Dr. Vitti will address this question.

DR. VITTI: Bob Vitti, Regeneron. The question was how many patients did not reach the week 52 visit and needed to have their data carried forward from week 40? And the answer is, there were 2 patients in the BUTTERFLEYE study that fell under this category, and none from FIREFLEYE.

DR. CHODOSH: Thank you.

DR. JONIAK-GRANT: Thank you.

DR. CHODOSH: Dr. Joniak-Grant, did you have any follow-up?

DR. JONIAK-GRANT: I don't. Thank you.

DR. CHODOSH: Are there any additional clarifying questions from anyone on the panel?

(No response.)

DR. CHODOSH: I'm not seeing any hands raised. Perhaps we should give a moment --

DR. CHAMBERS: No, there is.

DR. CHODOSH: -- okay; there's one.

Dr. Atillasoy?

DR. ATILLASOY: Hi. It's Dr. Atillasoy. Can you hear me?

DR. CHODOSH: Yes. Please go ahead, sir.

DR. ATILLASOY: Yes. This is Dr. Ercem Atillasoy from Jazz Pharmaceutical. I'm the non-voting industry rep. I do have a question for the agency, and a statistical question.

Both yourselves and the sponsor mentioned what I would call a relatively conservative margin for non-inferiority, so the question I had is, was there any consideration that the agency had of widening that margin, given the demonstration of efficacy, effectiveness, that we see here? I just was curious about that in terms of the thoughts around that; so just a question on the margin, and perhaps it was too conservative, and that may have been the issue, given what I view as a demonstration of effectiveness and safety. So that was the question.

DR. CHAMBERS: This is Wiley Chambers. In evaluating non-inferiority trials and non-inferiority margins, we will normally look for two

things. One, if we can find the equivalent of placebo-controlled or no-treatment controlled data, we will look to see what the difference is between that and the presumed active treatment, and we determine what's called an M1. An M1 basically tells you how much better you would be than no treatment or a placebo treatment.

We then try and preserve some of that because you don't want to have a treatment that uses all of that efficacy and basically puts you back at being a placebo. So we take a fraction of that, and that fraction is typically called M2. The M2 we also want to be clinically meaningful, and we want it to be what physicians would consider to be essentially equivalent treatments. And 5 percent, at least internally within the FDA, we believe physicians would call treatments that were equivalent. So we think the 5 percent was an appropriate margin for being an equivalent treatment. That said, it's smaller than the M1, so it still preserves some benefit over no treatment, but it is tight enough to say these two treatments

would determine whether the treatments were equivalent.

So we think the conclusion that the aflibercept treatment is not necessarily equivalent to laser but is superior to no treatment is appropriately justified from the data that we've received.

Does that answer your question?

DR. ATILLASOY: Yes, it does. I very much appreciate -- given the 2016 guidance, one of the examples the agency provides is the example of the 10 percent margin, but I agree and understand. Thank you very much.

DR. CHODOSH: Thank you. This is Dr. Chodosh again. We have a question from Dr. Chiang please.

Please go ahead, Michael.

DR. CHIANG: Jim, thanks. I'm sorry if my question is a little bit naive, and I'm not sure who to address it to. Maybe I'll address it to Dr. Chambers.

I noticed that all five of the presenters in

general spoke about anti-VEGF agents in the general sense; that it would be good to have anti-VEGF agents approved, whereas just hearing about one particular anti-VEGF, aflibercept. And it possibly may be the one that's used the least right now just because it's been validated, and the trial was the most recent of the trials.

Can you just describe the outcome of today and what the implications are going to be for other anti-VEGF agents that are out there?

DR. CHAMBERS: Wiley Chambers. At least within the field of ophthalmology, the most common reason -- or the answer that I most commonly give to the question similar to what you're asking, why a particular agent has not been approved for a particular indication, is because no one has submitted an application for that product for that indication. That is the case here, too. We we cannot approve products where no one has submitted an application requesting that indication.

In this particular case, we have Regeneron requesting that aflibercept be indicated for the

treatment of retinopathy of prematurity. It will have no impact on any other anti-VEGFs unless the particular companies that manufacture those products also ask for the indication. For any of them, we also would expect adequate and well-controlled trials to demonstrate that the product is safe and efficacious. That doesn't necessarily mean new trials, but it means trials need to be conducted that show the product is safe and efficacious.

DR. CHIANG: Thank you very much.

DR. CHODOSH: Thank you.

Are there any other clarifying questions from the committee?

(No response.)

Questions to the Committee and Discussion

DR. CHODOSH: The original schedule, of which we're well ahead on, had us taking a short break. But I think it's so soon after lunch, and I checked with Dr. Bonner, and we don't need to take a break unless I hear something dramatic from the panel. Therefore, we will now turn our attention

to address the task at hand, which is the careful consideration of the data before the committee, as well as the public comments we heard earlier.

We will now proceed with questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open to public observation, public attendees may not participate except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording, and then we will open the question to discussion.

I'm going to read the first question. Question number 1, and this is to the panel, discuss how the studied use of aflibercept in the treatment of retinopathy of prematurity can best be communicated to physicians and the caregivers of these premature infants? We will be following the raise-your-hand method, please, so that we can do this in an orderly fashion.

Dr. Joniak-Grant, I see your hand is raised. Please go ahead.

DR. JONIAK-GRANT: Hi. I'm going to focus on the caregiver part of this question. I'm also a parent of, fortunately, a late preterm infant but one that had complications, and as the parents mentioned, I think we have to think about this in two ways.

One, when you're in the hospital, and you're in the NICU, and you're dealing with everything, and then perhaps information later when you have been hopefully released and you're doing follow-up, you kind of focus on the hospital side of things.

I think one thing that's really important to remember in all of this is that parents, when you're in the NICU and things, children have multiple health issues, you have multiple specialists that are coming in and out all day long; you're having to make these sort of what feels like spur-of-the-moment decisions that have extreme impact on your infant; and you're there all day all the time because you never know when someone's going to show up at the door finally to talk to you.

So it's a lot of hurry up and wait, and then make quick decisions. You're tired, and for a lot of parents, this is the first time they've had to deal with anything really medically complex.

I think one thing we really need to think about is not just having to be solely dependent on your physician to fill you in, because I think you don't even know what questions to ask at those points, but maybe thinking about there being even handouts that are tables that can do some comparison charts of the benefits and risks of different approaches.

What does it look like long term in terms of follow-up in terms of frequency, length of time, some of the rates of recurrence, and just trying to make it into really a basic bullet-point table, I guess, of how to digest all this really complex information, recognizing that this person can't go and look things up because probably they're waiting to meet with the next specialist, and in line 30 minutes later to make the next decision. I think that's something that we have to be really

mindful of and aware of, and helping them have the tools that they need to make the decision.

On the other hand, I think it's also important that because there are a lot of unknowns, that those unknowns be communicated, but not in a way that it then puts the burden on the caregivers. Unfortunately, sometimes as things get more unknown, some physicians tend to say, "Well, you know, it's really up to you; you have to make the call," and that is an extremely difficult position for parents to be in. I think if there could be some way to help manage some of those details, it would be really beneficial.

DR. CHODOSH: Thank you, Dr. Joniak-Grant.

Dr. Chiang?

DR. CHIANG: I would say just a few things. Number one, as a physician myself, if I can just share my opinion, I believe having used anti-VEGF agents has allowed me to take better care of babies, and in my opinion helped prevent vision loss in some babies. That's just my personal opinion.

Now, in terms of communicating to the physicians, to answer the question, I think that for some physicians, there's a narrative, "Oh, I can just spend 5 minutes instead of 120 minutes," which is the data from these studies, but I think that really oversimplifies the burden on the physician. For me as a physician, I think the challenge is that the physician ends up needing to see the patient and follow up much more often, and then there's a very high chance that the physician ends up doing laser anyway because of peripheral avascular retina or because of reactivation. I think that needs to come across to physicians, that there's that trade-off.

I think the other thing is that for the caregivers, I think it's also really important to communicate that it's not just that 5-minute treatment that's a cure-all; that you will have to be committing to bring your baby back really pretty frequently and potentially be readmitted, and that the standard of care for that, which we discussed in the earlier session, is evolving. I don't know

that we have answers for when is the right time for treatment of disease reactivation or even what the threshold is that should warrant there's a treatment after anti-VEGF injections.

So those are my thoughts about issues that I think would help to communicate to physicians and also to caregivers.

DR. CHODOSH: Thank you, Dr. Chiang.

Dr. Clayton?

DR. CLAYTON: Yes. Janine Clayton. I think that one of the issues I'd like to bring up is the fact that -- and piggying back on what Dr. Chiang mentioned -- there are a lot of nuances and contingencies that go into clinical decision making, generally, and that is amplified in the setting of ROP.

In terms of this specific question, how to convey that best to physicians, I do think that a variety of means need to be employed to reach physicians. Case studies are one way to do that. And again, amplifying Dr. Chiang's message, that each decision isn't being made in isolation; it's

in a context of the overall care of that patient. I am heartened to hear from the family members and caregivers that this really is a challenging circumstance for them in terms of decision making, which makes it even more critical that clinicians have in mind a broader context -- which they do, of course -- and not just that individual injection or individual laser decision.

So the bottom line is I'd like to say that it would need to incorporate content that speaks to the overall outcome of the ROP for that particular patient, and shouldn't be just a single decision point. End.

DR. CHODOSH: Thank you, Dr. Clayton. Thanks so much.

I believe Dr. Murray.

DR. MURRAY: Thank you, Dr. Chodosh. My comment is that I believe that virtually all the retina specialists have an understanding of anti-VEGF use in ROP. I think that the issue here will be broadening that understanding outside of the retina community to our support caregivers and

our families.

Further, I'm interested in a comment on the potential unintended consequences of aflibercept receiving FDA approval for the use of a non-FDA-approved drug such as bevacizumab. Thank you.

DR. CHODOSH: Thank you.

Dr. Atillasoy?

DR. ATILLASOY: Yes. Ercem Atillasoy again, non-voting industry rep, and I speak on my own behalf and not on behalf of Jazz Pharmaceuticals. I do still represent the industry in general.

Just for a quick background for the audience and committee, I am a dermatologist by training. There are some points of connectivity. I have had a late-stage healthy preemie. I've had a father who had retinitis pigmentosa, so I know firsthand the devastating effects of retinal disease, so I really want to commend all the investigators and parents, and very heartfelt condolences to the Cundiff family. So I have clearly heard the devastation that retinal disease and loss of sight,

what the impact may be.

Therefore, just to state my own personal view, certainly the best way for the sponsor to communicate by regulation is, of course, for the indication to be approved so that we can have the best information provided to the physicians and caregivers to have a more informed discussion as opposed to the off-label use, so the compassionate use of the product.

So I just wanted to state the obvious. An approval of this supplement and the indication for ROP makes the most sense. So I just wanted that commentary. Thank you very much.

DR. CHODOSH: Thank you so much.

I still see a few hands raised. If you're done with your question, you can lower your hand so that we know that you're not making a second question.

Dr. Clayton, did you have an additional question or comment?

DR. CLAYTON: Sorry about that. No. Let me fix that.

DR. CHODOSH: Thank you.

Are there any other -- oh, I see Dr. Joniak-Grant's hand is up. Please go ahead, Elizabeth.

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant, and just more of a comment. I think in terms of a parent, the information that would be important I think is it's just mindful to say what we like to hear. I think the recurrence and the retreatment rates, and that laser would be possible, I think is helpful and what follow-up looks like.

I think the unknowns are a really important point. What is not known in terms of systemic effects, and what adverse event likelihood with multiple injections? That's not known. There were a lot of things we just talked about today that it's like, "Well, we don't know." I think that's all really important things that parents would want to know, and also to maybe think about -- and we can talk about this more with the next question -- possible contraindications, especially

in families that have bleeding or clotting disorders with the increased likelihood of hemorrhage; that impact.

I have von Willebrand, so I am forever dealing with that, with that side, and my husband has clotting stuff. So I think also parents would want to know that because these are some details that might not always come up in these types of consults.

DR. CHODOSH: Thank you so much.

Are there any other clarifying questions for this question number 1, or comments?

(No response.)

DR. CHODOSH: Okay. Before we move on, I'm going to just summarize what I heard as the chairperson. This is Dr. Chodosh again.

Dr. Joniak-Grant commented mostly on communicating to the caregivers and often the parents, but not always, and reflected that in the hospital setting with a premature birth -- to use my own words -- there's chaos, and decisions need to be made spur of the moment, and wondered what

sorts of materials could be provided to patients.

Dr. Joniak-Grant then later highlighted what we don't know and really what will follow, making sure that caregivers know about recurrence and retreatment rates, that laser is still possible, but understanding that no one has really determined what the perfect follow-up schedule should look like and how that should be individualized, et cetera.

Dr. Chiang commented that the availability of anti-VEGF medications off label has allowed him to take better care of babies, but he commented on our need to figure out how best to communicate to physicians because -- and I thought of this also -- it's not just a one-time injection, one and done, and it would be unfortunate if that was the message.

Dr. Murray qualified, I think, that providers who are currently doing this therapy will know because most of them are using off-label, anti-VEGF therapies, and they've learned that follow-up is needed. Dr. Murray also asked a

question as to what might be the unanticipated effects of approval of aflibercept on the use of other medications, perhaps unknowable.

Dr. Clayton highlighted there are lots of nuances to clinical decision making that in this particular scenario are particularly amplified, and that we need multiple -- in my own words -- and overlapping ways to communicate to physicians around this decision making. I think some of this might be reflected in the language that the FDA puts forward.

Dr. Atillasoy, as a family member of someone with retinal disease, commented on its impact on the individual and their family, and highlighted that just approving aflibercept for this indication would really mean improved communications to physicians based on the approval alone over its use, and would highlight the availability of this to caregivers.

I think the other comment that was made was the need to communicate this not just to ophthalmologists taking care of these babies, but

also to other physicians in the NICU environment about what it means for babies. But again, if it's already in common use off label -- and I don't have personal experience with that -- then perhaps that might be less necessary than we think.

With that, we're going to stop with question 1 and move, please, to the components of question 2. This is perhaps longer, but we're going to just go through all of these at once.

Our job is to discuss potential labeling, including, A, wording of indications and usage; B, wording of warnings and precautions; C, wording of dosing and administration; D, wording of pediatric use; and E, wording of the clinical trials section. I suppose we could probably pull up the document we had earlier if we need to.

Dr. Chiang's hand is still up, or its newly up; I'm not sure. But go ahead.

Dr. Chiang?

DR. CHIANG: Jim, I'm sorry to raise my hand again. I had a comment really about the previous question because I think that Dr. Murray raised the

point that was really important, and I just want to make sure that it gets emphasized. I think there are a lot of challenges here in terms of who the caregiver really is.

In ROP care, it's a little bit unique in ophthalmology in the sense that there's quite a few handoffs that occur. Very often a paradigm is that a retina specialist comes in, or a pediatric ophthalmologist will examine these babies week after week and then be the person who talks within the NICU team; and when they want treatment, they call somebody else to do the treatments, regardless of whether that treatment's anti-VEGF or whether that's laser. Then the person who does the treatment says something, and the person who does the treatment often has a different background. They're often the ones who know more about anti-VEGF, the long-term sequelae compared to, for example, the pediatric ophthalmologist, who's really the one who follows the child.

I think where this comes in the care is that the NICU team talks to, quote, "the

ophthalmologist," and they may not always know the nuance of which ophthalmologist knows what. Furthermore, in the medium, and in the even short term and long term, in a lot of cases many hospitals will have a situation where it's a different ophthalmologist every week, or every month, who examines, so there's so many handoffs in care.

I've seen enough cases in my career of miscommunications that occur when something got told to somebody or not everybody knows everything, so I think that just really emphasizes how important it is to have a consistent line of communication and whatever can come across in these labeling things, so that everybody hears kind of the same thing.

That came into my mind when Tim mentioned the point about that the treating doctor always knows, and I completely agree with that. And I think one of the challenges is that a lot of other people may not know, and I think that is sometimes the root of the problem.

DR. CHODOSH: Yes. In that context -- Dr. Chiang, thank you -- I wondered how the failure of the trial to meet a primary outcome of non-inferiority, as now must be written in the labeling, may generate concerns and confusion at numerous levels, obviously. But perhaps since it seems that most retinologists who give this care is already convinced, I wonder whether the biggest impact may be on families who choose to learn this information and whether it will reduce their confidence in therapy, and whether there might be some way in the labeling to emphasize that the therapy was clearly better than historical rates of no treatment to somehow buttress the failure of the non-inferiority trial to meet its endpoint.

As I was reading through it, I did have this pause in thinking when I read that, as to someone who perhaps doesn't understand the nuances that laser historically didn't do quite as well as it did in the trial, and that perhaps these particular trials -- again, looking retrospectively, looking now -- may have been underpowered and might have a

lot of pause about agreeing to anti-VEGF therapy or even perhaps create problems for physicians when things don't go perfectly with those babies.

I think it's a difficult question, and I have to say I really like and appreciate that the FDA convened the committee for the purpose of looking at labeling and communication because I think in this particular instance, that's where the really difficult decisions are going to be made, and it's going to have a downstream impact that I think may be pretty broad, so it needs to be done just right.

Dr. Joniak-Grant, please go ahead.

DR. JONIAK-GRANT: I think speaking to your point about how to phrase it, I'm not a fan of double negatives, so the way this hypothesis is written was stressful. But perhaps saying something along the lines of demonstrated and improved clinical course compared to untreated subjects, but not an improved course compared to those treated with laser photocoagulation; something like that would help clarify for parents,

and then obviously for parents to make the language simpler but have that be the general message.

DR. CHODOSH: Do you think, Dr. Joniak-Grant -- this is Dr. Chodosh again -- that it might be worthwhile to flush out the differences that were highlighted by some of the previous comments, that although the results being what they were, it appears to be efficacious -- the treatment -- that it would require perhaps additional follow-up, and perhaps more treatments, and perhaps even laser treatment at a later age, and then, again, qualifying that laser treatment at a later age would be expected to cause less peripheral vision loss, and perhaps be less likely to lead to myopia.

I mean, it gets really detailed, and that's the problem. This is not sort of a clean study outcome where you go and you say, "Oh, this is equivalent or better than existing therapy" because no one can say that here.

DR. JONIAK-GRANT: Yes. This is Elizabeth Joniak-Grant. I think that would be helpful. I

think that not writing things in long sentences is helpful. Putting them in bullet points is useful, because even reading through all of these documents and all the briefing documents, I didn't know if laser was -- I assumed it was still possible since it was done, but would it be possible after 3 injections? I didn't know.

So I think clarifying some of that information -- and there could be the benefit of less peripheral vision loss -- would be really useful information to have, and being clear, and not possible follow-up but definite follow-up, and what does that look like because we have to be mindful that there are people that live 3 hours from a facility that may not be able to get there, and what does that look like.

So I think we have to be really mindful, too, of what does that look like, and in daily life, how does that play out that these infants are getting the best care that they need?

DR. CHODOSH: This is Dr. Chodosh again. In New Mexico, it could be 8 hours from an individual

that can give care, depending on the financial situation for the family. So I agree, and perhaps the need for follow-up should be emphasized regardless of the decision. But it seems from the data that it's even more important with the use of anti-VEGF therapy than perhaps it might be with complete laser treatment.

We have gone back to question 1. Are there any other comments related to discussion of question 1?

(No response.)

DR. CHODOSH: No one's hands are raised. We allow you to come back if you wish, but can we flip to question 2 again?

Do any of you have comments, or questions, or concerns about the potential labeling?

Dr. Murray?

DR. MURRAY: Tim Murray, Miami. I think that Wiley's discussion and comments from the initial labeling in the comments were really spot-on, and that I think should target maybe how we move forward in that discussion. Thanks.

DR. CHODOSH: This is Dr. Chodosh again. I got a notice that the network was lost.

CDR BONNER: I can hear you, Dr. Chodosh.

DR. CHODOSH: Okay. It just came back on. I can't tell if that was local, Dr. Bonner, or whether it was here.

DR. CHAMBERS: It was local to you, because we didn't [indiscernible].

DR. CHODOSH: Okay. Alright.

CDR BONNER: We didn't have that. Yes, that's correct.

DR. CHODOSH: Okay good; not a surprise.

Alright. Please, everybody, hang on just a second because I have a request that I want to respond to.

(Pause.)

DR. CHODOSH: It looks like Dr. Joniak-Grant has raised her hand again, and we want to get to that.

I want to make sure that everyone on this panel understands that we're going to come to a point soon where if you have no further comments,

we're going to move back, and I may want to also allow Dr. Chambers to ask something more specific, if he would like, because I have the sense that we haven't really gotten very specifically to question number 2.

So let's first go to Dr. Joniak-Grant.

DR. JONIAK-GRANT: Thank you. Just a quick question as we move forward discussing this label. Is this essentially the label insert that only the physicians will see? Because if they're receiving the medication, I'm guessing caretakers will not be seeing any of this information.

DR. CHODOSH: Dr. Chambers, can you answer that question?

DR. CHAMBERS: Yes. This is Wiley Chambers. This is what's called the physician package insert. It is the basis for basically everything else. So any patient insert which is really not a -- patients obviously don't read this; at this point, it would be more caregivers. But anything that's in lay language, any advertising that's done, is basically derived from this.

DR. JONIAK-GRANT: Okay. Thank you. That's helpful.

DR. CHODOSH: Okay. I want to make sure -- this is Dr. Chodosh again -- that we fully address these questions so that the FDA has our opinions, so let's go through this one by one, then.

Indications and usage. Are there any comments about it?

(No response.)

DR. CHODOSH: This is Dr. Chodosh again. My personal view is that all that can be said is what the indications were for entry into the trial and how it was used.

By the way, Dr. Joniak-Grant, your hand is still raised. I don't know if you have an additional question. If so, please go ahead.

DR. JONIAK-GRANT: I do. Thank you.

One thing in the dosage and usage I noticed is that it said up to 3 injections may be administered, but it was noted that this is kind of an arbitrary number, and I think perhaps that

should be indicated because, at least to me, it reads as though that's just the normal protocol; that that is how we do this. So I think clarifying that is important. Thank you.

DR. CHODOSH: Dr. Atillasoy, you're next.

DR. ATILLASOY: Yes. I would recommend that perhaps we could pull up the slide the agency, Dr. Chambers, [indiscernible].

DR. CHODOSH: Thank you. I was wondering the same thing. Thank you.

DR. CHAMBERS: Slide 26 for my presentation. This is Wiley.

(Pause.)

DR. CHODOSH: It looks like we're getting there.

Slide 25? Was that correct?

DR. CHAMBERS: Twenty-six. Well, 25 is the indication, if you want to start there.

DR. CHODOSH: Yes, let's start there.

Go back one, please. Okay. This is it for indications? Okay.

DR. CHAMBERS: This is Wiley Chambers.

This is a relatively broad indication. It's not subclassified. It's all treatment of retinopathy. It's not written as has to be done in conjunction with something else. I'm not suggesting that it needs to be different than this; I'm just giving you the possibilities of what happens with some other indications.

DR. CHODOSH: This is Dr. Chodosh. So then my question is, since treatment was indicated for specific stages, does that need to be stated as an indication -- and this reflects my ignorance, perhaps -- or is it just retinopathy of prematurity?

DR. CHAMBERS: This is Wiley Chambers. So trials may be either the whole indication or they may be representative of the indication where you believe you can extrapolate to a larger population. Just because the trial was only done in lesions that were at a particular location does not mean you necessarily need to make the indication just that. The best example is a trial may include 34 year olds and 37 year olds. That doesn't mean

you say the trial was good for 34 and 37 year olds. You still put in 35 and 36 year olds.

DR. CHODOSH: Thank you, Dr. Chambers.

Dr. Atillasoy?

DR. ATILLASOY: Yes. Just from my view, this would be an agreeable indication. Later on, I think a discussion about perhaps an additional sentence in the clinical studies section, Section 14, would support the indication. I think we can come back to that issue, so I'll bring it up at that point. Thank you.

DR. CHODOSH: Thank you.

Dr. Murray?

DR. MURRAY: My comment for this is that retinopathy of prematurity is not uncommon, but treatment-warranted threshold retinopathy of prematurity is much rarer. So do we need to make it clear that this is not for the treatment of retinopathy of prematurity broadly, but only for threshold-warranted infants? Thank you.

DR. CHODOSH: Dr. Chambers, would you like to respond?

DR. CHAMBERS: Yes. This is Wiley Chambers. So basically, the permission is given to treat patients with this condition. That does not mean that everybody with this condition necessarily warrants treatment.

DR. CHODOSH: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Elizabeth Joniak-Grant. I'm not sure if this would be the area to include this information, but just that it was noted that the response rates were lower in infants with zone I ROP and the advanced progression ROP than in zone II ROP. I didn't know if that goes into the indications section or if that goes more into like the clinical trials section, or how that works, but I felt that might be worth noting.

DR. CHAMBERS: This is Wiley Chambers. That would normally be described more in the clinical trials section, unless you're saying it's only good for zone I or only good for treatment of zone II.

DR. CHODOSH: Great.

Dr. Murray?

DR. MURRAY: I'm good with that. I'm

looking at the next one and comment.

DR. CHODOSH: Dr. Lai?

DR. LAI: Yes, just a question for Dr. Chambers.

Currently, laser is an FDA-approved treatment of retinopathy of prematurity. I'm wondering if that is simply how the indication's left because, if so, perhaps we could do it the same way for aflibercept; that we understand, again, to give clinicians the maximum flexibility to use this treatment ROP, knowing that elsewhere we'll have data and guidelines on how more appropriately to use it.

DR. CHAMBERS: This is Wiley Chambers. I don't know the exact wording of all of the different lasers or that they're all even exactly the same. It would be laser-specific. It wouldn't be a general claim.

DR. CHODOSH: Dr. Chiang?

DR. CHIANG: I actually just lowered my hand because I had basically the same question as Dr. Murray, but if I can just maybe make another

point to that.

Wiley, I totally understand your rationale for leaving it as treatment of retinopathy of prematurity broadly, and I would be fine with that, but I just wanted to point out one comment for the record.

About 10 years ago, when people started using anti-VEGF agents, which was at the time of bevacizumab, there was some word on the street that people were beginning to treat more aggressively; in other words use anti-VEGF agents when they otherwise wouldn't, or potentially even when treatment wouldn't have been warranted, according to usual published guidelines. And the rationale for that was that it was, quote, "easier to do," so people were just doing it more often.

I saw some survey data at the time, or some data actually backing up that statement that I just made, and I don't know what current practices are like, and it's really hard to get that sort of data anyway. But I just wanted to say for the record that I think that Dr. Murray's comments -- I just

want to back up that I have some question about whether we should define that specific treatment-warranted disease, even if we leave it vaguely in the opinion of the examining ophthalmologist.

DR. CHAMBERS: This is Wiley Chambers. Well, it's why I brought the question up. You also need to consider, or may want to consider, what justification you would need, if it's indicated that way, for insurance company. In other words, if you make it very vague, what are you contemplating would be the information that a clinician would need to have?

DR. CHIANG: Wiley, just my opinion, it's complicated to attach specific criteria in the instructions about what your cutoff for treatment should be just because there's always room for individual clinical judgment, and standards of practice may change over time based on new data.

I feel that the options would be, A, leave it as is, treatment of retinopathy of prematurity, or B, make it something to the effect of treatment

requiring retinopathy of prematurity, or something like that just to specifically say that it's treatment of severe retinopathy of prematurity or some modifier, just to indicate that there is a threshold, but leaving the threshold for the individual clinician to interpret for themselves when a baby needs treatment.

DR. CHAMBERS: This is Wiley Chambers. I agree with you. I just didn't want to put something that was vague that caused additional problems in the definition since I couldn't define what the specifics would be.

DR. CHODOSH: This is Dr. Chodosh. In thinking about it, as long as the clinical trials section is explicit, I think that the indication here is appropriate and allows some flexibility later, as opposed to having to change this as we learn more about it. If you make it too specific -- in fact, there may be future trials with new information.

When I look at this, I always think, well, wow; does that mean that you can take a 20-year-old

who technically has retinopathy of prematurity but is out of the treatment age and give them this drug? That would be a bit absurd, and I think it's up to the insurers, obviously, to determine what they want to pay for and what they don't; and the clinical trials section being very explicit and detailed could already be a problem since it wasn't shown to be noninferior. So they may decide that they don't want to cover it, but that's a different discussion than we're having today.

Dr. Atillasoy, did you have a further comment?

DR. ATILLASOY: Yes. I just wanted to comment briefly also just for background. I'm a physician in industry. I've headed up product labeling for large sponsors. I think the intent, as I said earlier, is that this is U.S. prescribing information, so it is directed at the physicians. I do commend the agency for what would be a broad indication in this case.

One of the things that we all collectively need to ensure is that the labeling does not become

obsolete; so beyond laser therapies, there could be a change in another modality and another device approved, so sometimes becoming too specific or too narrow can be problematic. I do think some of the discussion -- I want to make sure we don't commingle issues. This is for the prescribers. Many are on the call. Then other information and guidelines, those are derivative, and some of that's really outside the purview of the sponsor.

So I just want to make sure that we stay focused on the topic, but I do agree with the comments that have been made about, I think in this case, the benefit of the proposed indications, so thank you.

DR. CHODOSH: Thank you, Dr. Atillasoy.

This is Dr. Chodosh again. I think to summarize 2A, wording of indications and usage, the consensus is that this broadly stated indication is appropriate.

Let's discuss the wording of warnings and precautions, and maybe we can see those slides.

Dr. Chambers, it would be the next slide or

the one after.

DR. CHAMBERS: The next one was dosage and administration.

DR. CHODOSH: We're on warnings and precautions, so we stay in order. We can jump, I suppose.

DR. CHAMBERS: Alright, but your choice.

DR. CHODOSH: Okay. Let's go to dosing and administration because that's what we're looking at. Are there comments by the committee about this particular language?

I'll start. This is Dr. Chodosh still. I like that you added some flexibility to scheduling because people do have personal schedules and care for their children, and physicians also have schedules that might make the 28-day limit an obstacle, actually, if there's no availability on days 29 through 35, for example. And I agree that there's not enough information to limit the treatment up to one year.

So that's my my personal feeling. I was happy with this.

Any other comments? Dr. Murray?

DR. MURRAY: I have two major comments. It says, in total, up to 3 injections per eye may be administered from treatment initiation. I would just say retreatment may be required because some of these children may potentially even need more than 3 injections in that eye to achieve control, and we have seen that clinically. We've also seen local ROP recurrent activity at 2 weeks.

So I think that we might want to think about not limiting to a 25-day window for reinjection if we see activity. Those would be my two comments. Thank you.

DR. CHODOSH: Thank you, Dr. Murray.

Dr. Chambers, do you have any response to that?

DR. CHAMBERS: No, that was one of the reasons for -- this is Wiley Chambers -- putting this up. The three is what was done in the trial, but it's not that we've seen safety problems with the three, so eliminating it, I would view --

(Crosstalk.)

DR. CHAMBERS: -- [indiscernible] supported.

DR. CHODOSH: Dr. Chambers, there are sustained levels of bound drug antibody. As your treatments get closer together and add up, would you have some concern about systemic downside if you eliminate any particular number of injections or time frame entirely?

DR. CHAMBERS: I don't have any data to say -- personally, I'm concerned that if we were to go less than 2 weeks -- I don't know that I have any of the curves. The falloff systemically is fairly rapid over the first couple weeks.

DR. CHODOSH: This is Dr. Chodosh. So is there enough scientific data to choose a date shorter than day 25, then, as Dr. Murray might be suggesting?

DR. CHAMBERS: This is Wiley Chambers again. The problem is I don't know at what level there is a safety issue.

DR. CHODOSH: This is Dr. Chodosh. I assume that what happens -- and I'm not a caregiver in this particular venue; I'm a corneal specialist. I

assume what may happen is that insurance authorization is needed. So if Dr. Murray, for example, is seeing a patient who he believes needs a second treatment at 2 weeks, this would have perhaps an impact on his ability to get the medication for the patient; and then getting back to an earlier comment, made earlier in the day, about the unanticipated impact on use of other off-label medications, lightly, to mixing and matching, which could have other anticipated effects as well.

I'm not sure who's next. I think Dr. Lai might be next.

DR. LAI: Thank you. I just want to make a few comments echoing what Dr. Murray said earlier.

Number one, it seems that, as we learned earlier, 3 injections was an arbitrary number that we'd take in the trial without any scientific basis. I'm not sure that number needs to be in the dosing and administration part of the labeling. Then with respect to the dosing interval, I know I personally have encountered cases in the past where

I needed to consider retreatment within a shorter time interval than 25 days.

I think when one considers what's the rationale in even putting an interval in the labeling, I think some here have alluded to the concern about systemic drug level being stacked on top of one another, although there's little data in the literature about whether that actually leads to any documented cases of systemic toxicity.

I think the other rationale I'm kind of weighting is basically to assess the efficacy of the injection, and typically we would know, within a week or two, if the anti-VEGF injection has done anything. If it has, we should see signs of regression or improvement on the clinical exam. So I don't think it's unreasonable for a clinician to consider retreatment as early as 2 weeks out.

Then lastly, as Dr. Murray had raised concern earlier, the 0.01 milliliter dosing, the dose of aflibercept used in the trial may be on the low side. And if that were the case, then it would support the notion that in some patients with

extremely severe and aggressive ROP, a second dose may be beneficial as early as 2 weeks out; so thank you.

DR. CHODOSH: Thank you.

Dr. Joniak-Grant?

DR. JONIAK-GRANT: Thank you. Elizabeth Joniak-Grant. Yes. I mentioned earlier I'm fine with the 3 injections coming out. I do have concern with saying there's a need for more treatment at 14 days, and therefore we should reduce the limit to 14 days. We don't know the systemic impact. We don't know the potentiality for that. And you have to remember we're coming from a place where lots of things they thought wouldn't have systemic impact, especially on infants, turn out that they do, and they don't show up for a few years.

So I just want to proceed with caution with that a bit, and be mindful that until we have this data of some of the outcomes further down the road, if there are any, that we want to be mindful and not just pick a date because it's convenient in

clinical care, but to also balance that against, okay, well what's our best estimate for when this has been processed systemically before we do more -- would this also increase antibody as well; could that be a possible unintended consequence? -- and be mindful that these are infants that are getting all kinds of other medications and have a lot of other things going on, so it's a possibility that there could be some interactions at times, too. Thank you.

DR. CHODOSH: Thank you.

Dr. Lai, did you have a follow-up?

DR. LAI: Well, sure.

We don't know specifically what the long-term systemic effect of aflibercept is in patients with ROP, but we know that worldwide we've been using anti-VEGF injections, namely bevacizumab, for over a decade, and I personally have followed patients that I treated more than 10-plus years ago. Now granted, my own personal sample is low, but when you survey the literature and consider the number of anti-VEGF injections

that have been given to this population, what's extraordinary is that there's little, if any, long-term systemic issues that we're aware of.

Granted, this is a population that's medically very complicated and can sometimes be very difficult to tease out if VEGF blockade leads to a certain systemic issue later on, but what's difficult to argue is that the visual benefit that's been seen on these patients has been so remarkable that, really, it's hard to think of very specific cases that are strongly linked to individual injections of these drugs in this particular setting.

DR. CHODOSH: Thank you.

Dr. Joniak-Grant, follow-up?

DR. JONIAK-GRANT: Yes. Thank you.

Dr. Lai, just to clarify, when you're saying it's been used for 10 years, are you saying with this infant premature population?

DR. LAI: That's correct. We began using off-label bevacizumab in ROP patients probably 10-15 years ago, and by we, it's not just doctors

in the United States, but also in other countries. There was a graph earlier that one of the speakers showed the increase in the use of anti-VEGF injections in this population, and both of those are actually off-label use of bevacizumab.

DR. JONIAK-GRANT: Okay. Thank you. That is helpful information. Thanks.

DR. CHODOSH: Thank you so much.

Dr. Murray?

DR. MURRAY: Dr. Murray, Miami. Yes, our first injection with an off-label anti-VEGF was in 2007, and there's extensive national and particularly international experience over the last 15 years.

For the label indication here, I would suggest that we use a 2-week retreatment interval. I think that is protective to our current knowledge, but also allows the treating specialist to be able to use an anti-VEGF within the guidelines of its indication. I don't want to hamstring treating specialists who feel the child needs to be treated and give them an arbitrary

follow-up when the child is clearly progressing; and that is always, in my experience, as being usually within the first 14 days. Thank you.

DR. CHAMBERS: This is Wiley Chambers. Can I ask 12 days, 13 days, 14 days, 15 days?

DR. MURRAY: Dr. Murray.

Wiley, you're always a troublemaker. I think the clarity of the timing is trying to weigh the potential risk against the potential benefit here, and I think, from my clinical experience, the earliest that I have retreated in the setting with anti-VEGF has been 10 days, without complication. Thank you.

DR. CHODOSH: This is Dr. Chodosh. Obviously, they're looking for what to write down, so specificity is the game here. They're responsible for these decisions, and that is what we're here to do.

I see that we have some additional comments. It looks like Dr. Lai wants to say something, and then Dr. Chiang will follow.

DR. LAI: Just a very brief comment, that

practically speaking, most of these eyes are examined on a weekly basis, and sort of the cadence of how the ROP screening is typically set up at most institutions. So I suppose intervals of seven would make sense practically, and 14 is not a bad number, although Tim has an experience of having to do this as early as 10.

I wonder if there's a way to say it to make it -- I don't think it's necessary to do it shorter than 10, and I think I would not do it longer than 14, just because there may be eyes that need to be retreated at that interval.

DR. CHODOSH: Dr. Lai, this is Dr. Chodosh. Could it be said, then, that in general, treatment would be expected no more often than every 2 weeks, but that clinical judgment might -- again, this is not final wording, but there might be exceptions to the interval or something like that, and the FDA can come up with a language that blurs that day a little bit to give the practitioners room to institute treatment should it be indicated in that individual baby?

DR. LAI: I think that would be reasonable, but I see a few other hands up, so I could defer to some of the other panel members.

DR. CHODOSH: Dr. Chiang?

DR. CHIANG: Just a question about the intervals. The point was made earlier that there's not a huge evidence base -- or maybe that's an overstatement -- for any specific day, 28/14, and my question is, do you need to list a date or could it be something vague? You had mentioned earlier maybe something like retreatment may be warranted. In other words, do we need to put a number?

DR. CHAMBERS: This is Wiley Chambers.

DR. CHODOSH: Go ahead, Dr. Chambers.

DR. CHAMBERS: Our experience comes from the adult indication, which we originally labeled as being monthly, and then received multiple reports of insurance companies denying coverage because people had given it at day 20 -- at day 30, and they said a month went 31 days. And when asked further, we had others that were being denied at 27 days because we were told, "Well, a month is

28 days." So to alleviate the confusion and allow for what we thought was flexibility basically weekly, we set 25 days for the adult indications, and that stopped the complaints.

DR. CHODOSH: I have a comment here. This is Dr. Chodosh. I don't provide this therapy, but it sounds like nobody would be making this decision certainly earlier than a week because it takes time to see the effect of therapy. So perhaps one of the retinologists on the phone can comment on that.

What's the earliest you would need to make a decision to retreat? Because first it was 28 days, then 25, and now we're at 14, and maybe 10. I personally think that there needs to be a date on here because we wouldn't want people doing daily injections of this. That would really raise my concerns about systemic drug build-up and the unknown unknowns regarding that.

(No response.)

DR. CHODOSH: Anybody who gives this therapy want to comment on what's the earliest they would make a decision to want to retreat?

DR. MURRAY: Dr. Murray in Miami. I would suggest that we typically would not make a decision to retreat within the first 7 days, so I think a 1-week retreatment interval is appropriate for virtually every patient we would see. Thank you.

DR. CHODOSH: Any others giving this treatment? Dr. Lai?

DR. LAI: Yes. I want to second that, and I do also want to echo Dr. Chambers' statement. That issue that he raised is something we deal with on a daily basis in my group.

When a patient inadvertently comes in one day too early because of a scheduling issue, if they're there in our clinic 27 as opposed to 28 days, we would have to either reschedule the appointment or use a sample because the insurance will not reimburse the anti-VEGF injection, even if there's clinical evidence of disease activity.

I just want to commend the FDA for recognizing that issue, and going through the effort of making it possible so that these babies aren't caught in that same situation.

DR. CHODOSH: Thank you, Dr. Lai.

At this point, I'm going to recognize Regeneron to speak. Typically during this part of the meeting, we do not have the sponsor speak, but we're going to make an exception with one slide and a comment, and be specific to the question of dosing and administration. Thank you.

DR. HIRSHBERG: Yes. This is Boaz Hirschberg. Just to add to the discussion, we can model the PK and work with the agency on the questions raised by the panel.

DR. CHODOSH: Thank you, sir.

So no further hands are raised. I'd like to summarize our comments on dosing and administration.

I think the focus was on the arbitrariness of the choices made for the clinical trial. We all know that we do clinical trials because we don't know the answer to something and that decisions have to be made that are often based on very limited data with regard to dosing frequency, et cetera. I think our discussion really, really

focused on that.

I think that Dr. Joniak-Grant raised the concern that I also raised about us not knowing the systemic impact of giving more frequent therapy. That was countered by those who cited greater than 10 years of giving other anti-VEGF medications without seeing those problems.

I would comment on that, that without really looking at registry data very carefully, I'm not sure that we would necessarily -- when you deal with a rare complication of a rare treatment, you compound the rareness, and it's very easy for complications to escape the identification of such by individual practitioners because if you see one case, you may not be stimulated to think that it might be due to a therapy that was given some time previously.

So I'm not sure that we can use case reports, small case series, or our own personal experience reliably to state that there wouldn't be a problem for more frequent dosing, but on the other hand, we also want to make sure that vision

is preserved. So it comes down to balancing the retention or preservation of vision versus an unknowable complication. I think we can have some assurances that it would probably be rare given the clinical experience to date.

That's my take on this discussion. I'm gratified that the sponsor will work further with the FDA on this particular language.

Dr. Chambers, what's next in your slide set? We can just go through these questions in whatever order your slides are in.

DR. CHAMBERS: There were other dosing and administration.

DR. CHODOSH: Okay. Let's look at those, please.

If I might -- this is Dr. Chodosh still -- I had a question about this. I'm not a retina specialist, but I am called on occasionally to give intravitreal injections, and as those amounts get lower and lower, the confidence that I have when pushing the syringe down to a certain mark and then delivering the drug, my confidence reduces as the

volume gets lower.

I don't really have an answer to this. It was just a concern about dosing errors, either not enough, which might lead to a need for early retreatment, or too much, which I think, after hearing from others about use of higher doses, I'm a little less concerned when I read the document than I am now.

I don't know if you have any responses to that. You're asking practitioners basically to push the syringe down to a very small mark on the syringe.

DR. CHAMBERS: This is Wiley Chambers. I have the same concern, although this is what was done in the clinical trial.

DR. CHODOSH: Yes.

Do any of those who do this in practice have a concern about this part of the instructions for use?

DR. MURRAY: Dr. Murray in Miami. I think that has been a concern with these small volume injections since we have begun intravitreal

injections. It's more of a concern when the volume becomes significantly smaller, as it is for this dose for aflibercept.

Having said that, I think there is a range, a therapeutic window, that we have, either to have a slight increase or a slight decrease in the delivered dose, and without having a differential preparation of aflibercept, specifically in this population, I don't see an alternative other than what we currently do. And most of us are comfortable that we can deliver an effective dose appropriately. Thank you.

DR. CHODOSH: Thank you, Dr. Murray.

I suppose that if the frequency of administration in the dosing and administration language is reduced -- and whether that's going to be, 14 days or 10 days, or whatever it's going to be, I don't know -- then that would relieve some of my concern about not giving sufficient medication because that could be an issue, right? You give an injection. It turns out that you didn't really give the injection or didn't give the full dose,

and then at the 1-week follow-up, you decide you need to do more.

Any other comments here? Dr. Joniak-Grant?

DR. JONIAK-GRANT: I don't see why you can't say -- I think it would be useful. You can say do not use the prefilled syringe, but then you could also say use the vial, and then in parentheses, see section blah, blah, blah, to kind of direct people where to go to find the information that they're looking for instead of going through the pages, and pages, and pages to get to the next information that they need.

DR. CHODOSH: This is Dr. Chodosh.

Can we look at the next slide or set of slides? Because I think what follows this is some instructions.

Dr. Joniak-Grant, does this address your concern? Because these are the instructions to describe how to do it in the absence of a prefilled syringe.

DR. JONIAK-GRANT: Yes. I think these instructions are fine. I think the biggest thing

that struck me with going through some of this is that there'd be a little information related to infants, and then you'd have to go through 4 or 5 pages to get to the next part that was related to infants, and then you had to go through more pages to get to the next part that might still be speaking to what you just read.

I think you start with dosage and administration, and you go through a number of sections; and you get to 2.6, which talks a little bit about prematurity; then you get to 2.7 that talks about the prefilled syringe; and you just have the note that says, "Do not use it," for treatment of ROP; and then you get the whole discussion of a prefilled syringe for many, many pages; and then you get finally to administration in preterm infants.

So I'm wondering if particularly in dosing and administration a section that just is addressing infants. And I would recommend for ROP maybe that the label have the section that has everything all in one place that people

need -- because there is so much information -- could be beneficial. But particularly with the dosing, I think it might be useful if it is all contained in one spot instead of a couple different sentences here and there, and then the meat of it several lines later.

DR. CHODOSH: Thank you.

Dr. Chambers, is it possible to segregate the ROP part, or should there be a C section, whatever, added to the previous don't use the prefilled syringe?

DR. CHAMBERS: This is Wiley Chambers. It's possible to do what was just described.

DR. CHODOSH: Okay. So we'll leave that for your judgment.

Can we go to the next slide, please? Any comments about this from the committee?

Dr. Lai?

DR. LAI: Yes. Maybe I'm being nitpicky, but when I do my injection, I do not aim the needle toward the optic nerve. The reason is because in the neonatal eye, the lens, it's proportionally

larger. It's larger in proportion to the volume of the eye compared to an adult. This would be a technique appropriate for treating an adult eye, but typically the way I was trained and the way I trained my residents and fellows, if the patient was supine and the eye was looking straight up, the needle should go perpendicular to the ground. It should go straight back to avoid hitting the side of the lens.

I wonder if others who do injections on this call feel the same way.

DR. CHODOSH: Dr. Murray?

DR. MURRAY: I think the concern is, with this extended indication, if non-trained intravitreal injection specialists were to inject, then this becomes very critical. So we need to have an understanding of the unique anatomy of these premature infant eyes, and I think that's what Dr. Chiang's alluding to.

I also would like to echo that having the specific instructions for ROP separated is important because if you were to read the dosing

and administration for injection in an adult, it would read very differently. If you injected one eye 1 millimeter from the limbus, you'd likely compromise the lens in that patient. So I echo the separation of the labeling, and I would agree that there is some issue with either contact with the lens during the injection or contact with the retina that are technique related. Thanks.

DR. CHODOSH: This is Dr. Chodosh.

Dr. Murray, how would you, quote, "say" this? Where should the needle point? If it's 1 millimeter from the limbus in a premature infant, how do you direct your needle? Is it simply perpendicular?

DR. MURRAY: I don't do perpendicular because you have the potential with less experience to actually contact the lens with that approach, and I don't want them to inject strictly straight at an angle because they can contact the retina. So typically you will aim at a space in what I consider the posterior vitreous, which is where you're looking -- and it depends, because we're not

telling people to inject temporally or nasally, and the anatomy differs from a nasal or temporal injection approach.

We recommend temporal injections typically just above or below the midline, and I'll have my fellows, where what I ask them to do is think of where the macula would be and inject in that direction. So it's a little temporal to the optic nerve and spares the lens and also spares the retina. But this is technique dependent and requires some significant training or experience. Thank you.

DR. CHODOSH: So do you think the needle pointing toward the optic nerve comments should be omitted entirely? Because it sounds like -- I thought of this, too, that depending on where you do the injection, your angle is quite different if you're aiming for the optic nerve, and that could either cause damage or perhaps a change in the outcome.

DR. MURRAY: Dr. Chodosh, I agree with you with that. That's exactly correct. This is not a

simple technique, and one of the things that has been commented on as we moved from laser -- which was complex and required expertise -- to intravitreal injection therapy, most people feel that that is a simplistic treatment and requires little experience, but in fact in these eyes, it's exactly the opposite.

So I think that the 1 millimeter is an appropriate point, but then the issue of how the needle is directed becomes key, and that differs from where you enter. So for me, it would not be perpendicular. It's an oblique angle temporally aimed toward the macula, which is just temporal to the optic nerve.

DR. CHODOSH: And because these eyes are so small, does there need to be something specific about the length of the needle?

DR. MURRAY: That's also an excellent comment. There is a needle that was designed specifically for use in ROP, and I think that was reported. And the uniqueness of that needle was that it had a shorter needle length from the hub of

the needle to the tip, and it was felt that that significantly lowered complications from injections. But for the majority of sites that are participating, I believe they do not purchase a specific needle for ROP, and that therefore becomes the concern.

DR. CHODOSH: So then would it be best to have a distance into the eye? I think, to the degree that it is specific, it should be correct, and then the question is, is it specific enough to aid a practitioner? I think although it's unlikely in most circumstances that someone, aside from a retinologist or pediatric ophthalmologist, would be giving these injections, I can tell you in some environments, it's possible that someone else would be asked to give these, and we want it to be safe as possible, obviously.

DR. MURRAY: I think that's a critical aspect of this, and we train our injecting fellows to enter these eyes to no more than 2 millimeters from the needle tip. That allows them to clear the space in the injection site for pars plana/pars

plicata without compromising the lens or the retina. So it's the distance from the limbus; the approach, temporal or nasal; the angle of injection of the needle; and the depth of the needle. Those are all critical to a successful injection. Thank you.

DR. CHODOSH: Okay. Not to belabor this, so there's a level at which the detail becomes counterproductive, right? Because there may be people who differ, and then it creates a new problem. I don't have the answer to this, obviously, because this is not something that I do, or hope to do.

Any other comment about --

(Crosstalk.)

DR. MURRAY: I think --

DR. CHODOSH: Go ahead.

DR. MURRAY: -- the 1-millimeter from the limbus, I think that's a valid statement, and then maybe we do it indirectly by commenting that the needle should be directed to avoid the retina or the lens, and that way allows some disparity

between the injection approach of the injecting surgeon.

DR. CHODOSH: Thank you. This is Dr. Chodosh. It also would alert the practitioner, perhaps, who might not be thinking about that. I shudder to think that that could happen, but --

Dr. Chiang?

DR. CHIANG: Yes. My only comment about this is that what I've been seeing is that I think that there are a lot of differences, clearly, in what people are being taught and what people are teaching.

I think, Tim, what I'm hearing from you, you're about as close to the standard of care, I think, that anybody would say, but my comment is I feel like what we're hearing here is what should the standard of practice be for intravitreal injections in a neonate.

My question is just how much of that belongs on this sheet versus how much of that belongs in practice guidelines and other things, and is there a way where this statement here -- and should FDA

be defining the standard way to perform these? So that's really a question for Dr. Chambers, I guess.

DR. CHAMBERS: This is Wiley Chambers. So to the extent that we believe it's going to cause harm, we generally will include it. We're not generally trying to push standard of care per se. I do tend to like things like you're not hitting the lens and retina because there's clearly safety concerns, without getting into some of the specific techniques, which I think are better taught in programs than described in labeling.

DR. CHODOSH: Thank you.

This is Dr. Chodosh. I'm looking at the hands up, and I'm not sure who has failed to lower their hands. I think, Dr. Lai, you may have raised your hand again.

DR. LAI: Yes, I just wanted to follow up. I think what I would advocate is removing the phrase, "the needle pointing towards the optic nerve" because I think that's wrong, or that's incorrect. And I'd like your suggestion of perhaps just leaving it to say, "with the needle directed

at an angle that avoids injuring the lens and the retina." Thank you.

DR. CHODOSH: Thank you, Dr. Lai.

Dr. Atillasoy?

DR. ATILASOY: Yes. Ercem Atillasoy. I disagree with the commentary. I was looking at the product labeling, and there is a statement along the lines of for use with a qualified physician, so I might propose and suggest, given the commentary, perhaps some additional qualification there.

If that's something in this section for the label, I leave that question to the agency and the experts in this area. Should there be additional commentary about the qualification for use either maintained with a qualified physician or expanding that to slightly along the lines of either pediatrics, retinologists, et cetera? Just something for the agency, the sponsor, and the panel to consider.

DR. CHODOSH: This is Dr. Chodosh. I have a comment about that.

Dr. Atillasoy, with respect, I have a

concern about that just because in large urban centers, there are usually enough providers to take care of such things. For example, in my environment, getting ROP care, well, it's being done now, but if somebody retires or leaves, you can't really send a NICU baby to another city for their care.

I can imagine there could be circumstances in this country where a comprehensive ophthalmologist who has experience with intravitreal injections might be called upon to assist with these, and then the question is, what does qualified mean, and who gets to define that gets to the scope of practice, which might not be what the FDA wants to engage in.

So I don't know. I think it's a really good concern, and I guess it's a concern with every procedural drug that we give, that the person know how to do it, but I'm not sure whether that's in the FDA purview.

Dr. Chambers, do you have any comment about that as a discussion item?

DR. CHAMBERS: I agree with you. There's a middle ground that we generally try to follow unless there's clear safety -- we generally don't label things for particular titles of people. We expect people, by virtue of education and training, to be able to do skills, and that's the most we would normally label for.

DR. CHODOSH: Thank you, Dr. Chambers. This is Dr. Chodosh again.

To summarize, there was a lengthy discussion about the injection itself. I heard no disagreement with leaving 1 millimeter from the limbus. It's an important thing, particularly for those with less experience in the very small infants. And the idea that the needle should be directed so as to avoid injury to the lens and retina would at least alert the person reading this to think about it, which is really what we want them to do because they might be injecting nasally, they might be injecting temporally, and the actual direction then could be different, or the angle would be quite different if injected toward the

optic nerve with the nasal versus a temporal injection.

Can we go to the next slide, please? I think this corresponds to our question 2B, wording of warnings and precautions. This is simply a table. I imagine there are no comments or concerns about the issue of rounding.

Can we go to the next slide, please?

This is Dr. Chodosh again. I don't really have a suggestion. I had to change it. I think I reflected earlier my concern of how this was going to be seen both by insurers, and perhaps -- but maybe not by practitioners, who seem to be already convinced.

Can we see the next slide so I know what follows? I forget. Yes, you can go back.

Dr. Chambers, my question here would be -- and Dr. Joniak-Grant, you'll be next -- whether there needs to be something more because I suppose insurance might look at this and say, "You know what? Your trials failed. Why should we pay for this?"

I think that the intent here is to get an approved drug, or to get approval for an already marketed drug for this specific indication, and I wonder whether the language here could better reflect that intent because it's almost like, well, we're going to approve this, but it didn't really seem to work as well as laser, or it wasn't as good as laser. It wasn't inferior, but it wasn't non-inferior. And for the average person and the insurance company making those judgments, I'm not sure they'll appreciate the subtleties.

Don't respond to that yet, Dr. Chambers. Let's hear from Dr. Joniak-Grant first.

DR. JONIAK-GRANT: Hi. Not just insurance; I would say most people that aren't statisticians. I've taught sessions on statistics, and even the way it was worded, I had to stop for a second and think. And people are pressed for time, so I think definitely making a point of trying to remove the double negatives, trying to say it failed to demonstrate, and putting it in more language that demonstrated an improved clinical course compared

to untreated subjects, and then FDA and you all can weigh in, but not an improved course compared to those treated with laser photocoagulation.

It's hard, because I wonder if extra specifications, at times when -- is it more advisable in certain situations to use this over laser, for example? Would it be worthwhile to include that? Is this not the place for that? That's definitely where I have to turn to all of you who deal with this in your daily lives.

One quick thing is there was the adverse event slide that we saw briefly. Are we going to come back to that --

DR. CHODOSH: We certainly can.

DR. JONIAK-GRANT: -- or are we sort of past that? Okay. If we could come back to that later after we discuss this, I would appreciate that. Thank you.

DR. CHODOSH: This is Dr. Chodosh. Sure.

Dr. Chambers, would you like to comment or respond to what's been said about this slide?

DR. CHAMBERS: Wiley Chambers. So it's

there for discussion for exactly the reasons you're not talking about it. There is not a requirement when we approve a product that it be the best that is available, and the question comes up, do we in this section -- we're obviously going to talk about the comparison in the clinical trials section. It does not necessarily need to be described in the pediatric use section that it failed to demonstrate non-inferiority. We usually do try and describe the rationale for the use, but we're certainly open to a variety of language.

DR. CHODOSH: Yes. This is Dr. Chodosh again. Thank you.

Dr. Atillasoy, you had your hand up briefly. Would you like to say something?

DR. ATILLASOY: Yes. I would recommend, as was stated, that either it's moved, it's relegated to clinical studies Section 14.6 or, one, the agency and panel could consider just a slight rephrase, essentially detaching the two, that there was failure to demonstrate non-inferiority.

Yet, it certainly is very clear -- my

understanding from the presentations and all of the data, it's really clear that obviously a placebo-controlled study would have been unethical. It's clear to me that there is a high rate of effectiveness and efficacy from the studies, and therefore you can detach the two sentences and maybe make a brief statement about the efficacy rate seen.

So I would just perhaps detach using the word "while" there because I think that "while" sort of connotes either change the sequence to bring up the failure of non-inferiority, then mention the efficacy, or just, as Dr. Chambers mentioned, move it all to 14.6.

I do think, based on the conversations we've had and the public session, it's really important that there is some brief statement about the efficacy and the effectiveness of the product. I mean, clearly, there are other sources of data that the sponsor has. I'm sure they have aggregated some, such as the compassionate use, so it's pretty clear there are other bases for evidence or

effectiveness. So at least one sentence in the clinical studies section should suffice and address the concerns about what I understand now, the insurance issues, so thank you for that.

DR. CHODOSH: Thank you. This is Dr. Chodosh.

Dr. Durham, you have your hand up.

DR. DURHAM: Yes. I would agree with the last comment, so I wanted to endorse the concept of using the word "expected natural history" since no one made an attempt here to do a direct comparison versus the historical control rates.

DR. CHODOSH: Thank you.

Dr. Chambers, are you still on?

DR. CHAMBERS: I am.

DR. CHODOSH: Okay. Sorry. We couldn't see it.

I think in summary here, there were concerns about this particular section, and I like the idea very much of just stating what the results, the efficacy was in the trial. I don't know whether you're comfortable with saying that these rates

were similar to those with laser, but the concern is that this may undo the purpose of approving this drug with regard to getting insurance so that the drug can be used and covered by insurers. As to how to parse that language exactly, that's why they pay you the big bucks, I guess.

Can we go back one slide, please?

Dr. Joniak-Grant, what was your question or comment about the slide?

DR. JONIAK-GRANT: My question with this was the adverse reactions. I had two things. One was that we discussed how due to the smaller sample sizes, the risks were somewhat unknown with how they change with an increase of additional rounds of injections, and that is something, definitely as a caretaker, I would want to know. I'd want to know it as a patient, too, especially if I had a physician that was maybe more aggressive in trying to do multiple ones.

That was my first comment on that, and my second one was here, with the adverse reactions being a bit higher with the hemorrhaging and

things, should there be any warning or precaution about -- and this is for all of you who are medical doctors, any notes about contraindication if a family history of sickle cell anemia or von Willebrand's disease, or those types.

I don't know if that would impact this and cause more risk for hemorrhage. I don't know how those mechanisms would work in the situation, but that we're calling out so people are aware that those are the main differences from laser.

DR. CHODOSH: Thank you. I'm going to take those two, so I'll leave it up to Dr. Chambers about any knowledge of the interaction between intravitreal injections and bleeding disorders, in a general way, and perhaps there are others on the call who want to comment.

I think perhaps, Dr. Chambers, a note could be added to this that these data reflect somewhere between 1 and 3 injections over 52 weeks, and that the adverse reactions in patients who are given more injections, that they were no more than 28 days apart. So there could be a footnote in the

top section to reflect how these injections were actually given, because this is cumulative, I believe, for the 52 weeks.

So if that's true, then I think it's helpful to the practitioner to know that, at most, these were 3 injections given over that time period, and that the side effects or the adverse reactions associated with more injections and more frequent administration are unknown.

Dr. Chambers?

DR. CHAMBERS: This is Wiley Chambers. We certainly can look into what other qualifications we put along with the table. Conjunctival hemorrhage is, in general, not a concern, even with most bleeding disorders. Retinal detachment you know tends to occur late, so differentiating whether that's based on the first, second, or third injection would be difficult.

Intraocular hemorrhages clearly are more of a concern with individuals with bleeding disorders. That's sort of the reason for even listing them, as if you know you have a bleeding disorder,

potential, there is more concern for an intraocular bleed.

DR. CHODOSH: Yes, and I guess my comment, Dr. Chambers -- this is Dr. Chodosh again -- is based on the assumption, which I think most would agree with, that the more times you inject the eye, the more adverse reactions you're likely to see. So if your injection caused a retinal detachment in a direct way, that would be very unfortunate, but that rare complication would be more likely the more times a needle goes in the eye.

The same thing for hemorrhages, pressure, defects, all of these side effects theoretically, adverse reactions, the numbers would be -- so if you gave 3 injections, or 1 to 3 injections, as I assume this data means, you would see a certain rate, but if you gave 12 injections, for example, over a year, you would expect higher numbers of these.

That's why I think it's worthwhile to emphasize that these rates reflect a particular trial procedure, and that the practitioner should

know when they look at these numbers that lenticular opacities of 1 percent may not be the case if they inject every 2 weeks for months. That might be obvious, but maybe not.

With regard to the bleeding, it wasn't clear to me the difference between a conjunctival hemorrhage and an injection site hemorrhage. Maybe injection site hemorrhage is more localized, but I don't know how the study would differentiate that. I assume injection site hemorrhage means externally, but maybe not.

Can you comment on that?

DR. CHAMBERS: Wiley Chambers. I honestly don't remember the --

DR. CHODOSH: Okay.

Dr. Joniak --

DR. CHAMBERS: If you want an answer, I would ask the sponsor for what the distinction was.

DR. CHODOSH: Dr. Joniak-Grant, you have a hand up.

DR. JONIAK-GRANT: Yes, and this is the last thing on this; perhaps something about long-term

safety data is still being collected. It's seen as important enough to do it --

DR. CHODOSH: Yes.

DR. JONIAK-GRANT: -- and if this is the info that trickles down to caretakers, I think that's important to know.

DR. CHAMBERS: Wiley Chambers. We certainly can do that, as well as, Dr. Chodosh, your suggestion of qualifying the table. We can do that, too.

DR. CHODOSH: This is Dr. Chodosh.

Dr. Joniak-Grant, I think that's really an excellent suggestion because it lets everybody know there may be more information than contained in the table, and that was my goal also.

Can we go two slides ahead, please?

Does anyone disagree with removing this information in this section? I'm looking for hands raised.

(No response.)

DR. CHODOSH: Going once, going twice. Okay.

Next slide, please. Any comments looking at hands?

DR. CHAMBERS: This is Wiley Chambers. I'll just point out, because of the discussions, and we were having discussions earlier, you see what the systemic concentration was at day 1 versus day 28 in each of the two trials, and see how dramatically it falls off over the month period.

DR. CHODOSH: But we don't have the day-by-day study -- this is Dr. Chodosh -- of what that curve looks like. I don't know if the sponsor has that data to know or not.

I see Dr. Joniak-Grant, and then Dr. Chiang will be next.

DR. JONIAK-GRANT: I agree that having more info about how it falls off, especially if we're talking about having it not recommended but allowed earlier, would be useful. I also wonder if it would be useful to put in the information about where adults line up to give some contextualization, because you read this, and you say, "Okay, well that's great, but what does that

mean?" And perhaps being able to compare it to the adults would give people some frame of reference when they look at this.

DR. CHAMBERS: This is Wiley Chambers. There was a different section that has the adult pharmacokinetics. It's in the same label.

DR. CHODOSH: Thank you.

Dr. Chiang?

DR. CHIANG: Actually, that was my same question. I think it would be useful to know whatever is possible about what these numbers actually mean. Thanks.

DR. CHODOSH: Okay. This is Dr. Chodosh. I don't think we heard anyone suggesting that this be changed, and it sounds like this is about as granular as it gets for this particular trial. We don't really know the relationship between pediatric or neonatal levels, particularly in the premature neonatal levels and adult levels, and they might be quite different. So I would be concerned about extrapolating too closely from adult levels.

Can we go to the next slide, please?

I think that Dr. Joniak-Grant raised an earlier concern about what more frequent dosing might do to antibodies. It could go in any direction, based on my scientific American understanding of immunology, in that more frequent dosing might actually have the reverse effect or it might increase.

So I guess, Dr. Chambers, the only thing here might be to add the comment as to how the doses were given so that if there was a maximum of 3 doses given, at the least, this far apart over 52 weeks to generate this data, I think that helps interpretation because, otherwise, you sit there and say, okay, the antibodies are not a problem, and when you're not thinking about something, you don't see it; so letting practitioners know that the data was limited by the specific protocol in the trial.

The conclusion here shouldn't be, I don't think, that EYLEA does not induce antibodies; that the conclusion should be that under this dosing

schedule and actual dose, the antibodies were detected in less than 1 percent.

DR. CHAMBERS: This is Wiley Chambers. The majority of this paragraph is not from the pediatric studies, but it's from the multitude of studies in adults.

DR. CHODOSH: Right.

DR. CHAMBERS: It really has not been an issue in a wide variety of different settings.

DR. CHODOSH: I'll leave it to your judgment. I was thinking of saying, similarly, in pediatric ROP studies in which dosing was at 4 milligrams per -- or in these particular studies, the two studies that are cited here, dosing was at 4 milligrams, given no more than 3 times during a year, and then it qualifies it.

DR. CHAMBERS: And we can certainly do something like that.

DR. CHODOSH: I can think about it. I'm not sure whether it's absolutely necessary, but that's what I would do if you thought there was any reason to be concerned. Thank you.

Can we go to the next slide, please?

This is Dr. Chodosh. I think this may relate to E, wording of clinical trials section. If anybody has concerns about the wording, or questions, or comments, please raise your hand.

Dr. Durham?

DR. DURHAM: Yes. This is Todd Durham. My comment has to do with previous discussion, which is what's been tested here as randomized initial treatment to EYLEA versus laser, with the option at the investigator's discretion to use a second treatment or even a second modality.

I acknowledge Dr. Chambers in his presentation referenced the fact that for secondary outcomes, for the statistical plan, you typically don't include the data for the secondary, but my thought is that caregivers, parents especially, would find it very useful to know -- i.e., anticipate -- that a successful outcome that is shown in this table is also made up of study participants in whom a second treatment, or third treatment, or even a rescue treatment was

administered. So I wonder if it's possible either to include it as a separate row just as a descriptor or in some of the text or footnote.

DR. CHODOSH: Dr. Chambers?

DR. CHAMBERS: Yes. This is Wiley Chambers. As you point out, it is integral to some of these success rates, so I think it may make more sense to describe potentially what also could have been used to come up with these rates. We'll certainly figure out how to incorporate more of that.

DR. CHODOSH: Thank you. This is Dr. Chodosh.

Can we go forward in the slide set, please? Next slide. Okay. Sorry. Go back one. I'm sorry.

This is Dr. Chodosh again. It's hard for me to see what you would want to change here. This is very descriptive from the trials.

Anyone going to comment on this?

(No response.)

DR. CHODOSH: Not seeing any hands, let's go to the next slide, please.

This is Dr. Chodosh. If I moved too fast and you feel we've missed something, please just raise your hand, and we'll go back. I don't want to shortchange anything.

Dr. Atillasoy, please?

DR. ATILLASOY: Just one minor comment on the first slide of the clinical studies. In looking at the product labeling, most of the sections are explicit saying the number of studies, so I would just add "determine the first slide, two studies" also, so it's clear to the reader that it's the original. It's the first slide in this section of clinical studies.

We don't have to go per se, but just to say "two." The other indications have the words, like two studies, because I think it will also be helpful given that I'm not sure the audience, the reader, will know what the difference is between FIREFLEYE and FIREFLEYE NEXT, so it would be helpful to add the word "two" there, "in the two studies" in that first sentence.

DR. CHODOSH: Okay. Any comments on this

slide? This does show the two studies' names.

(No response.)

DR. CHODOSH: Next slide? Again, very descriptive.

Next slide? And again, this is the data. There's not much to say about it.

Dr. Atillasoy, are you still -- your hand is still up.

DR. ATILLASOY: Just on this slide I was going to comment, if it's ok.

DR. CHODOSH: Yes.

DR. ATILLASOY: I think, based on the prior discussion we were having in the pediatric section, here's where I'd recommend the consideration of an insertion of one sentence. That should help better define the efficacy outcomes we see below in the table; so something along the lines of -- just to address the discussion we had earlier, Dr. Chodosh.

Here's where it might be an opportunity to add a sentence, a summary sentence, about efficacy in the context of natural history and things like that just to consider -- insertion here or

subsequent to this just so that we address the discussion we had earlier with regard to the pediatric section. Thank you.

DR. CHODOSH: Thank you.

Would it be fair to say after that EYLEA was not demonstrated to be noninferior, again, with double negatives that clearly triggered Dr. Joniak-Grant, as it does me? Should it then be said that both treatments are far superior to no treatment, or something to that effect?

Dr. Chiang, you have a comment?

DR. CHIANG: Yes. My comment is something that came up earlier in the morning discussion, and I know it's going to be difficult because this is the way the study was written up and published. But I feel like this comment, this row of patients with absence of active ROP and unfavorable structural outcomes, the phrase "active ROP," I just think is misleading because I think what active ROP really means is treatment requiring ROP, and I don't know if that's changeable at this point.

But I feel like that really would describe more of what actually -- and the reason I think it's important is that the community is still working out what to do with babies who have disease that didn't regress fully or with retina that remains avascular; in other words, not fully vascularized. So I'd just love if you could consider that.

DR. CHODOSH: Dr. Joniak-Grant?

DR. JONIAK-GRANT: Yes. I think it would be really useful -- and we did, as Dr. Chiang mentioned, talk about this a little bit earlier -- to include in the clinical studies information section that the recurrence rates, the retreatment rates, that 7 to 14 percent needed laser rescue, and that the response rates were lower in infants with the zone I ROP and the AP-ROP versus zone II.

There was something that really caught my eye in going through the briefing documents that said that the anti-VEGF therapy, when compared to laser, causes disease regression to occur faster,

and that has a higher likelihood of disease reactivation.

I think having some of those details and also recurrence. They mentioned most recurred within 16 weeks, but then some were within 6 months, but then an indication that this does not preclude recurrence after 6 months to kind of help manage that follow-up.

I think these are the details that are really important, and these are the details, in particular, that I want to see trickle down, especially to caretakers. And as I'm reading some of the labeling right now, I feel like a lot of those important pieces are missing.

DR. CHODOSH: Thank you.

This is Dr. Chodosh again. We heard from Dr. Chiang the question of what does active mean, and the suggestion that perhaps even though that wasn't in the published literature for this study, that it should be changed to ROP requiring further treatment. And then Dr. Joniak-Grant brought up something that I think gets to the first question

we've discussed on communicating to physicians and caregivers with a little bit more granularity.

I agree with that a lot. The thing that really struck me in reading all this was the idea that EYLEA in the studies seemed to get a more rapid response that was less associated with some of the feared complications of laser such as loss of peripheral vision and high myopia, but also required increased alertness for recurrence, meaning more follow-up visits, and that there were burdens to each of those, and that families would have to decide, unfortunately, on which burdens were manageable and which were not, and to help physicians understand that in communicating to patients what the potential benefits and risks were, would need that more granular information.

Dr. Joniak-Grant, did you have something else to say? Your hand is still up?

DR. JONIAK-GRANT: No. It's just a long day, and and I'm getting forgetful. Thanks.

DR. CHODOSH: I'm with you on the long day; long here, too.

Does anyone else have any comments about these discussion questions?

(No response.)

DR. CHODOSH: Barring that, Dr. Chambers, what among the things that we discussed are you still left wanting to hear from those that are, more than me, experts in this particular field that would be helpful to you? What's still sitting for you unanswered that you were hoping to get out of this full day?

DR. CHAMBERS: This is Wiley Chambers. I think this has been very helpful. We will look into a number of the points that were made in this last series of discussions. There is some difficulty -- some of the things that people may like to have pointed to are not statistically significant, which means they could have happened by chance, and we generally don't put things that are trends as opposed to definitive statements. We'll look back into what we think we can and cannot do.

I also hear what Dr. Chiang is talking about

as far as having an endpoint that is really treatment requiring ROP. That's always difficult to put as an endpoint because you can't say an endpoint is treatment requiring to evaluate a treatment. We usually try and describe it in terms of actual anatomic features as opposed to saying it's treatment requiring because that's frequently a judgment call, as well as sometimes based on socioeconomic factors, not just anatomic findings, but we'll relook at that language.

I think you've covered everything we were expecting, so besides just thanking everybody for their time, I don't know that I have anything else to direct you to.

DR. CHODOSH: Does anyone else on the panel, barring Dr. Chambers for the moment, have any other comments about today, about the process, or about the specific task?

(No response.)

DR. CHODOSH: Dr. Chambers, any last comments outside of what you just said, and thanks?

DR. CHAMBERS: No. I'm just going to

repeat, we very much appreciate the time and effort that everybody has put into reviewing this and your comments and suggestions, and we will take all of that into account as we have further discussions with Regeneron on potential language.

Adjournment

DR. CHODOSH: Thank you, Dr. Chambers.

As chair, I'll take the prerogative to echo that. First of all, I know how difficult it is to take an entire day from work, and as all of you on this committee did, I very much want to call out your service, because it is service.

I also want to recognize the FDA and Dr. Chambers and his crew for what has always appeared to me to be a highly collaborative process. Unlike what you might read about in the newspaper with regard to medication approvals, my experience with Dr. Chambers and his team has always been that they strive very hard to serve the public, and it's not about creating obstacles, but it's about doing things in a proper way so that the public gets what they need, with as much safety

along with that as possible. So I really appreciate you, Dr. Chambers, and your whole team, and I thank the committee.

I want to thank Dr. Bonner, who did an excellent job keeping me on track and avoiding major mishaps for me through our personal chat; and to the sponsor, thank you for your excellent presentation and for your work on a rare but critically important disease.

So with that, I'm going to adjourn this meeting. We will now adjourn the meeting. Thank you very much. Have a great evening.

(Whereupon, at 3:56 p.m., the meeting was adjourned.)