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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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67TH MEETING OF THE CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE

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October 12, 2017
8:30 a.m.

FDA White Oak Campus
10903 New Hampshire Avenue, Room 1503
Silver Spring, MD 20993

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M E E T I N G

(8:35 a.m.)

DR. BYRNE: Good morning. My name is Barry Byrne. I'm delighted to chair this morning's Advisory Committee meeting of the Food and Drug Administration regarding the product being considered today. And I wanted to just welcome the members of the Panel, all the participants, both here in person and viewing on the webcast.

And we just -- I want to take a moment to introduce all the panelists, too, to you. So why don't we begin with Lisa, if you could introduce yourself?

DR. BUTTERFIELD: Good morning. I'm Lisa Butterfield from the University of Pittsburgh.

DR. BROOKS: I'm Brian Brooks. I'm the Clinical Director of the National Eye Institute.

DR. CARNEY: I'm Marcia Carney. I'm presently at the Veterans Administration, Fayetteville, North Carolina.

DR. CHIORINI: John Chiorini, NIH Senior Investigator with NIDCR.

DR. EMERSON: I'm Geoff Emerson, a retina specialist in Minneapolis.

DR. FLOTTE: Terry Flotte, University of Massachusetts Medical School.

DR. HAWKINS: Randy Hawkins, internist and pulmonologist in Los Angeles, California, member of the Medical Board of

California.

DR. ZHU: Yao-Yao Zhu. I'm the clinical reviewer for this BLA. I'm presenting. Thank you.

DR. CHAMBERS: Wiley Chambers. I'm a supervisor, a medical officer in Ophthalmology with the Center for Drugs, FDA.

DR. BRYAN: Wilson Bryan. I'm Director of the Office of Tissues and Advanced Therapies in the Center for Biologics at FDA.

DR. ZOVEIN: Ann Zovein, University of California, San Francisco.

DR. WU: I'm Joseph Wu at Stanford University.

DR. WEST: Constance West, pediatric ophthalmologist, Boston, Massachusetts.

DR. RAASCH: Tom Raasch at Ohio State University.

DR. PLUHAR: Liz Pluhar, the University of Minnesota.

DR. MASSOF: Bob Massof, Johns Hopkins, Wilmer Eye.

DR. LEE: I'm Brendan Lee, a pediatric geneticist and Chair of Genetics at Baylor College of Medicine.

DR. LAI: Michael Lai. I'm a retina specialist at Washington, D.C., and Chief of Pediatric Retina at Children's National Medical Center.

DR. HUNSBERGER: Sally Hunsberger, biostatistician at NIH, NIAID.

DR. BYRNE: So thank you all for being here. And now

Prabha Atreya, who's the Designated Federal Officer for this project, will read the information regarding members' participation and Conflict of Interest statements.

DR. ATREYA: Good morning, everybody. I hope you can hear me. My name is Prabha Atreya, and it's my pleasure to serve as the Designated Federal Officer for this 67th Cellular, Tissue, and Gene Therapies Advisory Committee meeting. The Committee Management Specialist for this meeting is Joanne Lipkind, who is at the reception, and the Committee Management Officers are Marie Keller and Jeannette Devine. And I'm also helped by alternate DFO, Captain Serina Hunter-Thomas, in the room.

On behalf of the FDA and the Center for Biologics Evaluation and Research, we would like to welcome everyone to this meeting. Today's session has one topic that is open to the public in its entirety. The meeting topic is described in the *Federal Register* notice that was published September 11, 2017.

The FDA CBER press media representative for today's meeting is Ms. Andrea Fischer. She is in the audience.

And, Andrea, if you are here, please now stand up so people can recognize you.

And you can reach out to her if you have any need to speak about the media requirements.

The transcriptionist for the meeting today is Mr. Tom Bowman from the Free State Reporting, Incorporation.

I would like to remind everyone to please check your pagers and cell phones and make sure they are either turned off or in silent mode. However, whenever you are making your comment, please first state your name and speak up so that your comments are accurately recorded for the transcription as well as heard by the members of the public and those listening via webcast.

Now I'll proceed to read the Conflict of Interest Statement for this meeting.

The Food and Drug Administration is convening today's meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

At this meeting, in the open session, the Committee will discuss and make recommendations on the safety and effectiveness of Biologics License Application (BLA) Number 125610, submitted by Spark Therapeutics Incorporation. The topic is a particular method involving specific parties.

The following information on the status of this Advisory Committee's compliance with federal conflicts of interest laws, including, but not limited to, 18 U.S. Code Section 208 of the Federal Food, Drug, and Cosmetic Act, is being provided to participants at this meeting and to the public. This Conflict of Interest Statement will be available for review at the registration table outside.

With the exception of the Industry Representative, all participants of the Committee are special government employees (SGEs) or regular government employees from other agencies that are subjected to the federal conflicts of interest laws and regulations.

Related to the discussion at the meeting, all members and consultants 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 spouse or minor children and, for the purpose of 18 U.S. Code 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

FDA has determined that all members of this Advisory Committee are in compliance with federal ethics and conflicts of interest laws. Under 18 U.S. Code 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts of interest when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

However, based on the agenda and all financial interests reported by members and consultants, no conflicts of interest waivers were issued under U.S. 18 Code 208.

Dr. Dale Ando is serving as the Industry Representative to this Committee. He's employed by Gene Editing and Gene Therapy Consulting. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the Committee. Industry representatives are not special government employees and do not vote and do not participate in the closed sessions, if there any.

Also, Dr. Randy Hawkins is serving as a Consumer Representative to this Committee and is present at this meeting. He is appointed as a special government employee and is a temporary voting member and who will bring consumer perspective to the Committee. Consumer representatives are screened for potential -- their financial conflicts of interest and cleared prior to their participation.

At this meeting there may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals are not screened by the FDA for conflicts of interest.

FDA encourages all other participants to advise the Committee of any financial relationships that they may have with any firms, its products, or if known, its direct

competitors.

We would like to remind members, consultants, and participants that if the discussions involve any other products or firms not on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs 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 firms that could be affected by the Committee's discussions today.

Thank you for your attention, and this concludes the Conflicts of Interest Statement. Now I will turn the meeting over to Dr. Barry Byrne, our Chair for today.

DR. BYRNE: Thanks very much, Prabha.

So the topic of today's meeting is to discuss voretigene, the biological licensing application submitted by Spark Therapeutics. This product is for the treatment of patients with vision loss due to biallelic mutations in the RPE65 gene with retinal dystrophy.

So to introduce the topic, I'd like to ask Dr. Wilson Bryan, who is the Director of the Office of Tissues and Advanced Therapies in CBER, to begin the FDA introduction.

DR. BRYAN: Good morning, and welcome on behalf of the FDA, the Center for Biologics Evaluation and Research, and the

Office of Tissues and Advanced Therapies.

The science of genetics and the understanding of the human genome have been progressing rapidly. These scientific advances have brought hope that gene therapies may address many devastating illnesses. Today, the FDA is asking this Advisory Committee to discuss voretigene neparvovec, which is proposed as a treatment for patients with vision loss due to RPE65 mutation-associated retinal dystrophy.

This is a rare, inherited, devastating disease. It causes blindness with no available treatment. For many of us, this is exactly the type of disease that we hoped that gene therapy would someday treat. However, our enthusiasm for the promise of the field of gene therapy must be balanced by careful consideration of the data.

This product's primary evidence of effectiveness is based largely on a novel endpoint. We are uncertain whether the product's activity, as demonstrated by an effect on this novel endpoint, represents a true improvement in the lives of patients.

Therefore, our first question asks the Committee to discuss the clinical meaningfulness of this novel endpoint. Our other questions to the Committee focus on identifying an appropriate target population, focus on repeat administration of the product, and on the overall balance of benefits and risks.

We are truly grateful to the scientists and other professionals who have brought this product to this stage of development. And we are also grateful to the patients and their caregivers who participated in the clinical trials that will be discussed today.

The FDA thanks the participants in today's Open Public Hearing. It is critical that we hear from patients and patient advocates, particularly regarding the benefits and the risks associated with this product. Many individuals are not able to be here today, and we appreciate and will carefully consider the written comments that we have received regarding this product.

We want to thank all of the members of the Committee who have given their time in order to participate in today's discussion. I also want to thank all the members of the FDA review team and the Advisory Committee staff who have worked tirelessly to prepare for today's meeting.

I now turn to Dr. Byrne to continue with the agenda.

DR. BYRNE: Thanks so much, Wilson.

Well, we'll begin with a presentation from Dr. Katherine High, who's the President and Head of Research and Development at Spark Therapeutics.

So, Kathy, if you want to come up. Thank you.

DR. HIGH: Good morning. I'm Kathy High, President and Head of R&D at Spark Therapeutics. We are excited to be here

today to present the results from our development program for voretigene.

In our presentation today, I will provide an overview of voretigene. Dr. Mark Pennesi will discuss the unmet need for patients with RPE65 mutation-associated retinal dystrophy. Dr. Kathleen Reape will review the study design and efficacy results. Dr. Deborah Kelly will review the safety data. And Dr. Albert Maguire will conclude the presentation with his clinical perspective.

We also have several additional key experts available to help answer your questions. All external experts here with us today have been compensated for their time and travel.

The data we will present support that a single subretinal injection of voretigene into each eye improves functional vision and visual function in patients with confirmed inherited retinal dystrophy due to biallelic RPE65 mutations.

This is a progressive inherited disease that eventually leads to complete blindness in nearly all patients, and there are currently no treatment options that improve vision or help delay the progressive vision loss.

For patients with RPE65 mutation-associated IRD, voretigene therapy supplies a functional copy of the RPE65 gene within the retinal pigment epithelial cells, allowing for restoration of the visual cycle.

Let me briefly review the mode of action. From an

anatomic perspective, the defect is in the RPE cells shown here in gray. These cells form the blood-retina barrier and serve as nurse cells to the rod and cone photoreceptors. The photoreceptors are some of the most metabolically active cells in the body and require the support of the RPE cells to execute their metabolic program.

From a biochemical perspective, the visual cycle begins when light strikes the photoreceptors. 11-cis retinal is converted to all-trans retinal, and this begins the series of reactions that convert light into electrical signals, that travel along the optic nerve and eventually to the visual cortex.

The trans retinal is transported back to the RPE cells, where under the action of RPE65, cis retinal is regenerated. In the absence of RPE65, the visual cycle is broken, and vision loss results.

In this disease, the retinal anatomy is preserved for a relatively long period, which means that supplying the missing enzyme can result in restoration of the visual cycle and improvement in vision.

Before I leave this slide, I will note that we're targeting the apical surface of the RPE cells, as shown by the blue arrow, where there are cell surface receptors for AAV2. We're supplying the cDNA and coding RPE65 through the use of an AAV2 vector.

We chose AAV2 vectors because they efficiently transduce RPE cells. This, combined with the fact that AAV2 is the capsid with which there is the greatest clinical experience, makes AAV2 an excellent choice for this product candidate.

The voretigene expression cassette drives the expression of a wild type cDNA for human retinal pigment epithelium 65 kDa protein or RPE65. An expression is driven by a strong promoter enhancer.

The voretigene manufacturing process is specifically designed to yield a product that is essentially all full vector particles without empties. Voretigene is manufactured using triple transfection of HEK293 cells. The downstream purification separates empty AAV capsids from full AAV capsids so that only full particles are administered in the final product, an important consideration when vector is administered into a small area where the total number of receptors may be limiting.

The vector is formulated in a physiologic buffer containing a surfactant to prevent loss of vector on product contact surfaces.

Based on our Phase I studies, the recommended administration regimen is sequential, bilateral, subretinal injection of 1.5 times 10 to the 11 voretigene vector genomes delivered in a total subretinal volume of 0.3 ml per eye.

The individual administration procedures to each eye are

to be performed at least 6 but no more than 18 days apart, in order to identify potential early emergent surgical complications prior to the second eye administration procedure. The near-simultaneous administration to both eyes helps reduce the risk of an immune response. The area for injection is identified based on clinical evaluation including imaging.

Let me briefly review the regulatory history that reflects the evolution in the understanding of RPE65 mutation-associated retinal dystrophy.

In 2008 voretigene received orphan drug designation for the treatment of Leber congenital amaurosis due to RPE65 mutations. In June 2011 the FDA held an Advisory Committee meeting to discuss cellular and gene therapy trials for the treatment of retinal disorders.

Key recommendations included the need for novel endpoints tailored to the disease and associated clinical deficits and the importance of using multiple tools that can measure visual function and functional vision, as well as consideration of patient-reported outcomes related to activities of daily living.

This led to a series of discussions with the FDA, and our study design incorporated suggestions made by the FDA. The Phase III study began in 2012. Given the high unmet need and the promising initial clinical results, voretigene was granted breakthrough therapy designation in September 2014.

In November 2016 voretigene was given an additional orphan drug designation for treatment of inherited retinal dystrophy due to biallelic RPE65 mutations. This was based on an evolution in knowledge about genetic classification of inherited retinal dystrophies, including diagnosis and treatment, which you will hear more about from Dr. Pennesi.

The clinical development program for voretigene included, in Phase I, first, a dose escalation study and, second, a follow-on study testing the safety of injection of the contralateral eye. The Phase III study was the first randomized controlled Phase III study of a gene therapy for a genetic disease. All of these subjects have been enrolled in a 15-year follow-up study.

You will hear about two additional non-interventional studies: the first, a clinical study to evaluate the validity of the primary endpoint, a mobility test, and the other, a retrospective chart review to establish the natural history of RPE65 mutation-associated retinal dystrophy.

Our presentation will show that supplying a functional RPE65 gene resulted in clinically meaningful and statistically significant improvements in functional vision, light sensitivity, and visual function, compared to controls. Improvement was observed as early as 30 days, and the response has been maintained throughout the follow-up period for a period up to 3 years in original intervention subjects, with

observation still ongoing as of the BLA data cutoff.

Based on the durability of Phase III data, we are not recommending repeat administration. Additionally, we have not studied this in clinical development, and there are theoretical risks involved with repeat administration.

The safety profile was consistent with this type of administration procedure, and the safety data include patients followed for up to 9 years.

The proposed indication for voretigene is for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy. In addition to confirmation of the genetic diagnosis in a CLIA-certified laboratory, patients should have sufficient viable retinal cells by clinical examination and OCT.

Our labeling will indicate voretigene administration is appropriate for patients 3 years of age or older.

Thank you for your attention, and now I would like to invite Dr. Mark Pennesi to the lectern.

DR. PENNESI: Good morning. I'm Mark Pennesi, Associate Professor of Ophthalmology and Chief of the Ophthalmic Genetics Division at the Oregon Health and Science University. The focus of my research and clinical practice is inherited retinal dystrophies, or IRDs, which is why I'm excited to be here today.

My presentation will provide an overview of RPE65

mutation-associated retinopathy. I'll then explain how we evaluate vision in these patients and the impact of this disease. Let me start with the disease.

Inherited retinal degenerations are caused by a collection of over 250 different genes and result in an overlapping spectrum of visual dysfunction, with different onset, severity, and presenting phenotypes. Prior to genetic testing, there were many different ways to categorize IRDs, but we're now finding that the best way to classify these is by the causative gene.

The focus of this presentation will be one of these genes, namely RPE65, which is responsible for about 7% to 9% of Leber congenital amaurosis cases and about 1% to 2% of retinitis pigmentosa cases.

Biallelic mutations in RPE65 prevent regeneration of the rod visual pigment. The hallmark of this disease is rod photoreceptor dysfunction, resulting in nyctalopia, or night blindness. This can significantly limit a patient's ability to navigate in dimly lit areas such as restaurants or a crosswalk at night.

Cone photoreceptors, which mediate daytime and color vision, are secondarily affected. Patients describe their ability to see as like wearing multiple pairs of sunglasses even on the sunniest of days. Eventually, nearly all patients will progress to complete blindness.

Studies estimate that there are approximately 1,000 to 2,000 patients affected by this disease in the United States. Many patients will manifest symptoms in early childhood, but some patients are not identified until later, when parents notice that they have a difficult time in dim conditions or frequently bump into things.

In a natural history study of this disease, about half of the patients were diagnosed with Leber congenital amaurosis while the remainder were diagnosed with a variety of other terms. Regardless of what we label it, this is a severe, progressive disease that leads to complete blindness in nearly all patients.

Moving on to how we evaluate patients with this disease, we have many different ways to measure visual function, such as visual acuity, visual fields, contrast sensitivity, and dark adaptation. However, many of these tests present challenges in patients with RPE65 mutation-associated retinopathy because many of these patients are young and have poor fixation.

Rather than only look at tests of visual function, it's important to also look at functional vision. Functional vision represents how well the brain is able to integrate these different dimensions of visual function to accomplish tasks, such as reading, mobility, and navigation.

Let me now transition to the impact of RPE65-related retinopathy. Because RPE65-related retinopathy is so rare,

there was limited data on the natural history of the disease. To better understand the severity in disease progression, a retrospective natural history study was conducted based on charts from 70 patients with confirmed biallelic RPE65 mutations. Here are the visual acuity results, by age group, from the natural history study.

Even at an early age, almost no patients have 20/20 vision. In fact, many patients are approaching the level for legal blindness, and vision gets progressively worse with time. By age 16, half of the patients have reached the level of legal blindness, and by age 34, all have reached this level.

Similar progressive results were observed with regards to peripheral vision, as measured by visual fields. Here is a schematic illustration of how visual fields in one patient progressed over time. And while this is useful, it doesn't really capture the functional vision from a patient's perspective.

Let me show you a simulation of what a patient with this disease would experience. Imagine a crowded daytime situation, as seen here by a normally sighted individual. Patients with this disease may experience impaired central vision and decreased color contrast.

Now layer on top of that the visual field loss and the continued progression with time. It's obvious how one with this disease would have a hard time with normal activities of

daily living.

Here is the same scene of what a normally sighted individual may see at night. The situation gets even worse for these patients at night because they essentially have no rod function. And when you factor in the visual field loss, this gets even worse.

In order to illustrate the challenges faced by patients with this disease, let me show you a video of a study patient prior to treatment, trying to navigate the course used by the Sponsor by following the arrows on the floor.

As you can see, in both time and accuracy, the patient has a very difficult time getting through the course. Imagine what it's like for this patient to try to walk through a crowded school hallway or cross the street at night.

I'm going to stop the video here, as it takes almost 3½ minutes for her to get through the whole course.

In summary, patients with RPE65 mutation-associated retinopathy suffer from a severe and progressive retinal disease. More than 50% are legally blind by age 16, and all are legally blind by age 34. Furthermore, most of these patients will go completely blind.

Unfortunately, there are no available treatments, leaving patients severely limited in their independence. This can affect their education, career choices, and lead to social isolation. Clearly, an important and urgent medical need

exists for these patients.

We know this disease results from loss of function of the RPE65 protein. Gene therapy holds promise for restoring functional RPE65, thereby increasing retinal sensitivity, resulting in better functional vision. Such changes will improve the patient's ability to navigate safely and accurately as well as help them gain independence.

It bears repeating that without treatment, these patients have no hope for improvement and will go legally blind, and most completely blind. Physicians like myself are frustrated by our inability to help these patients.

Thank you for your time. I'll now invite Dr. Reape to the lectern.

DR. REAPE: Good morning. I'm Kathy Reape, Head of Clinical R&D at Spark. Today I'll review the clinical development program and Phase III efficacy results for voretigene.

Overall, the data demonstrate that treatment with voretigene in a randomized controlled Phase III study resulted in clinically meaningful and highly statistically significant improvements in functional vision, light sensitivity, and visual function.

These improvements were observed as early as 30 days after administration and were maintained up to 3 years, with continued observation ongoing.

Before revealing the results from our Phase III program, I'd like to describe the multi-luminance mobility test, or MLMT. The MLMT was developed to address the need for an endpoint relative to the specific symptoms of this disease. It was standardized during Phase I and selected as the primary efficacy endpoint for Phase III.

The MLMT was developed after discussions with the FDA and was designed to measure functional vision or the ability to perform everyday tasks. In this case, the task involves navigating a course, independently and accurately, within a pre-specified time limit.

Multiple factors contribute to navigation and mobility. The MLMT integrates input from visual acuity, visual field, and light sensitivity. Existing tests of mobility did not include changes in environmental illumination, and they were more simplistic, and they were not specifically designed to measure the clinical deficits in this patient population.

The test was designed for both pediatric and adult populations. It's conducted at seven different light levels, from 1 to 400 lux, spanning a wide range of everyday lighting conditions. It was important to include varying light levels since patients with RPE65 mutations have a decreased ability to perceive light, which may directly impact their ability to navigate using only their vision.

So let's take a look at how this test is conducted. The

test pre-specified benchmarks for light intensity using seven calibrated light levels, representing common, real-life lighting situations. The light range ran from a bright light level of 400 lux, as found in an office environment, down to a level of 1 lux, corresponding to the illumination of an indoor night light. The midpoint is 50 lux, as found at an outdoor train station at night.

The three pictures show relative light intensity for the same room layout, to give you a visual representation. Each light level represents about a half log change in light intensity. There were 12 different standardized MLMT course configurations, all covering the same distance and including the same number of turns and obstacles.

The patients were instructed to start at the first arrow, follow the arrows around the course, avoid all obstacles, and touch the doorknob at the end to complete the test. Patients must navigate the course at each specified light level evaluated, using only their vision, within a time constraint, and with a minimum number of errors.

At each visit, MLMT testing was conducted to determine the lowest light level at which participants could obtain a passing score for the right eye alone, the left eye alone, and then both eyes together.

Each test was videoed and sent for independent central scoring by two trained graders. If necessary, an additional

grader was used to adjudicate the scoring. Readers were masked to treatment assignment and study visit. MLMT tests were evaluated in random order, and random quality checks were performed during the trial.

Graders reported on a number of individual testing components and also generated an overall final result that included both accuracy and time components for each individual test. The MLMT was evaluated as either a pass or a fail, depending on whether the patient could or could not navigate the course within the time limit and with a minimum number of errors at the light level being tested.

Accuracy was based on the number of obstacles hit and the number of times the patient deviated from or missed the directional arrows. The maximum allowed number of errors for a passing score was three. The maximum time allotted for a passing score was 3 minutes, which included pre-specified time penalties for errors and redirections. In order to pass, patients needed to achieve both the accuracy target as well as the time target.

Next, to quantify patient performance over time, the MLMT score change was used. Each of the seven light levels was assigned a numeric score from 0 to 6. The MLMT score change was the difference between the score for the lowest light level passed at baseline and the score for the lowest light level passed at Year 1.

For example, if a patient was able to pass the MLMT at 50 lux but failed at 10 lux, the baseline score would be 3. At one year, the same patient now passes at 1 lux, which has a score of 6. Therefore, the MLMT score change would be 3.

We also assessed the MLMT in a separate, non-interventional study in normal-sighted and low-vision individuals with inherited retinal dystrophies to confirm its utility. This study was designed to characterize the construct and content validity of the test.

The MLMT performance between normal-sighted and low-vision participants was compared over a 1-year period. The relationship of MLMT performance to visual acuity and visual field was also evaluated. Twenty-six normal-sighted individuals and twenty-eight with IRDs completed the study.

Among the normally sighted participants, all baseline results were consistent through Year 1, and all were able to pass at the lowest light level of 1 lux. Among the patients with inherited retinal dystrophies, no improvements were observed at 1 year, and eight patients, or almost 30%, showed a decline in performance by one or two light levels at 1 year.

The MLMT exhibited threshold effects with respect to VA and VF, that is, performance declined markedly below certain levels for the visually impaired patients. For visual acuity, when the VA was 20/63 or better, passing scores were more likely to be obtained on the MLMT. Conversely, when the VA was

20/2000 or worse, MLMT tests were more likely to be failures.

Goldmann visual fields were measured in sum total degrees, with a higher value representing larger field of vision. For context, the range for normal-sighted individuals was 1,200 to 1,400 sum total degrees. For individuals with visual fields less than 500 sum total degrees, corresponding to approximately 40 degrees of vision, MLMT performance declined markedly, with more test failures.

This demonstrates that the MLMT integrates input from both VA and VF and shows that the test is sensitive to performance in a range relevant to the pathophysiology of IRDs. This study supports the use of the MLMT as a suitable endpoint for measuring functional vision in patients with inherited retinal dystrophies.

The results indicated that the MLMT could differentiate low-vision patients from normally sighted controls and could detect changes in performance over time. Importantly, the test could identify a wide range of performance among visually impaired patients, including some who declined at 1 year.

Across the entire clinical development program, more than 4,000 test videos have been evaluated, and high reproducibility has been shown. Construct and content validity were also demonstrated, supporting the use of the MLMT as a clinical endpoint.

Now, I'd like to turn to our Phase III clinical trial.

Our Phase III program was an open-label, randomized controlled study in which 31 patients with confirmed biallelic RPE65 mutations were randomized in a 2:1 fashion to either the intervention or control groups.

Patients were treated with systemic corticosteroids for 18 to 30 days in the perioperative period to minimize inflammation associated with the surgical procedure and to reduce the potential for an immune response.

Intervention patients received a subretinal injection of voretigene at a dose of 1.5 x 10 to the 11 vector genomes in a volume of 0.3 ml in each eye. Each injection was administered between 6 to 18 days apart. Efficacy endpoints were compared between the intervention and control groups at 1 year.

After 1 year of observation, all control patients then crossed over and received sequential bilateral injections of voretigene. We will refer to these patients after crossover as the control intervention group.

To be included in the study, patients had to be at least 3 years of age with confirmed biallelic RPE65 mutations. Patients had to have a visual acuity of 20/60 or worse, or a visual field of less than 20 degrees in any of 24 meridians for each eye.

Eligibility was also based on whether potential participants had sufficient viable retinal cells. All patients had to have the ability to comprehend the MLMT, follow course

instructions, and the capacity to successfully navigate the course.

In addition, patients could not have a passing score for any of the three eye-patching conditions at the lowest light level of 1 lux at the time of study entry.

The pre-specified primary efficacy endpoint was the bilateral MLMT score change at Year 1.

Secondary endpoints were also evaluated in hierarchical order: first, full-field light sensitivity threshold testing, or FST; second, monocular MLMT score change for the first injected eye; and third, visual acuity.

It was estimated that a minimum sample size of 24 patients, 16 intervention and 8 controls, was necessary to yield a simulated power of greater than 90% to detect a difference of one light level on the mobility test.

The primary analysis used a nonparametric permutation test based on Wilcoxon rank-sum test statistic, and the primary efficacy outcome was to be tested at a two-sided, Type 1 error rate of 0.05.

Thirty-one patients were randomized, 21 to the intervention group and 10 to the control. This made up our ITT population.

Prior to voretigene administration, two patients, one in each group, withdrew after randomization but prior to knowledge of treatment assignment. One intervention patient was

withdrawn by the physician due to surgical risks related to severe retinal thinning, and one control patient withdrew consent for personal reasons. This left 20 intervention patients and 9 control patients, which made up our MITT and safety populations. All 29 of these patients received bilateral injections of voretigene.

Here are the Phase III study demographics. The mean age at randomization was approximately 15 years old, with patients ranging from 4 to 44 years of age. Approximately 40% of patients were male, and the majority were white and from the United States. Finally, the average passing MLMT level at baseline was 50 lux.

The primary efficacy endpoint was performance on the bilateral MLMT as measured by the score change. The difference in means between the intervention and control groups was 1.6 light levels, which was statistically significant and clinically meaningful.

The first secondary endpoint was FST testing. The difference between the groups for FST was also significant.

The second secondary endpoint, monocular MLMT performance, showed significant results similar in magnitude to the bilateral MLMT performance, with a difference in means of 1.7 light levels.

The third secondary endpoint, visual acuity, using Holladay off-chart estimates, was not statistically significant

between intervention and control. Additionally, visual fields were analyzed as pre-specified exploratory endpoints and showed a nominal p-value of 0.006.

When looking at the totality of data across the Phase III program, we see a consistent benefit of voretigene therapy compared to control.

Let me now discuss each of these endpoints in more detail. All of the following analyses are based on the MITT population. Presented here are details for the mean bilateral MLMT scores over time. A score of 6 corresponds to a light level of 1 lux. Both groups started out with a mean score of approximately 3, indicating that the lowest passing light level was 50 lux.

Improvements in the intervention group of approximately two light levels were apparent as early as Day 30, and this difference was sustained over 1 year, while the mean change in control patients remained approximately 0 during this time.

At Year 1, all nine control patients crossed over and received bilateral injections of voretigene. As shown by the light blue dotted line, this control intervention group also experienced substantial improvements in functional vision.

Replicating the pattern observed in the original intervention group, these benefits were maintained through the first year after administration. The benefits observed at 1 year in the original intervention group continued through at least 2 years post-administration.

We are continuing to follow all patients in our clinical development program to assess the overall durability of response. In 2016, at the time of data lock for the BLA submission, 5 of the 20 original intervention patients had completed 3 years of follow-up, and the results remained stable, as shown here. To date, all 20 original intervention patients have completed 3 years of follow-up, with similar stable results.

We conducted an additional analysis of the time to completion of the MLMT. For the intervention patients, the average time to course completion dropped from just over 100 seconds to 49 seconds at Year 1, while the control group experienced virtually no change.

The clinical impact of more rapid navigation is easily grasped when considering commonly encountered activities, such as crossing the street.

Next, I'd like to return to the example of the child Dr. Pennesi presented earlier. On the left, we'll show the baseline video, where she fails the MLMT at 1 lux.

(Pause.)

DR. REAPE: Now, on the right is the same patient, 1 year post-voretigene administration at the same light level of 1 lux. This time she passes on both accuracy and time. Her performance in this video represents a one-light-level change on the MLMT.

Next, we analyzed the results of the primary MLMT endpoint by individual patient. Each point on the x-axis represents a patient from our Phase III program. On the left side of this chart we'll show the data from the original intervention group, and on the right side, we'll present data from the controls. On the y-axis, we will plot the bilateral MLMT lux score.

Let me walk you through the results for one patient before I present all of the data. The open blue circle represents this patient's baseline passing score of 2, or 125 lux. At 1 year, this patient was able to successfully navigate the course at 10 lux, which represents a two-light-level improvement.

Here are the baseline scores for each patient in the original intervention group. You can see that there was a range of baseline scores.

Here are the rest of the results for the original intervention group. We can see that 1 year after treatment, 19 of 20 patients experienced an improvement of at least one light level. Eleven of 20 patients improved by two or more light levels. Thirteen patients achieved the maximum possible score, meaning that they were able to successfully navigate the MLMT course at the lowest light level of 1 lux.

The figures in gold represent results from the control group during the year of observation. As I mentioned earlier, all control patients crossed over and received voretigene administration after 1 year. Here in light blue are the

results for the control intervention group 1 year after treatment. Eight of nine patients improved by at least one light level, and all of these patients achieved the maximum score of 6.

Summarizing the results for all patients 1 year after treatment, we see that 27 of 29 patients improved at least one light level, which represents a significant improvement in functional vision, and 16 of 29 experienced at least a two-light-level improvement on the MLMT.

Twenty-one of 29 were able to navigate the course at the lowest light level of 1 lux. For all 21 of these individuals, the maximum possible score was capped because the MLMT stops at 1 lux.

And as I mentioned earlier, in addition to successfully completing the course at lower light levels, the time to complete the course was cut in half.

Since the primary efficacy endpoint was statistically significant, the secondary endpoints were formally analyzed. The first secondary endpoint, full-field light sensitivity threshold testing, or FST, is a global measure of retinal sensitivity to light and a highly relevant endpoint for this rod-mediated disease.

FST showed a significantly greater than 100-fold improvement, on average, in the intervention group. The control group showed no change from baseline. For FST, the

benefits of voretigene therapy were again observed at Day 30 and continued throughout the first year of the study.

Similar results were again observed in the control intervention group, while the benefits observed in the original intervention group remained stable through at least 2 years.

Results for the second secondary endpoint, change in monocular MLMT performance, were also significant and showed results that were similar to the bilateral MLMT results.

The third secondary endpoint was visual acuity. The mean change from baseline to 1 year was 0.16 logMAR for the intervention group, corresponding to an eight-letter improvement on an eye chart. Although visual acuity in the control patients remained unchanged at 1 year, the difference between the intervention and control groups was not statistically significant.

One year post-administration of voretigene, the control intervention group experienced a change of 0.09 logMAR, corresponding to an improvement of 4.5 letters. Visual acuity for the original intervention group remained stable at 2 years.

In addition, as pre-specified exploratory endpoints, we analyzed visual field tests. Overall, following voretigene administration, both the original intervention and control intervention patients showed increases in sum total degrees, for the Goldmann visual field, with gains of approximately 300 and 200 sum total degrees respectively. Note that the

improvement in VF crossed the threshold of 500 degrees observed in the mobility test validation study.

Finally, I'll present findings from our visual function questionnaire. This was a pre-specified exploratory patient reported outcome measure.

The visual function questionnaire used in Phase III was based on the National Eye Institute VFQ-25, which was modified to be appropriate for a pediatric population and for patients with extreme low vision. There are 25 questions pertaining to activities of daily living. Patients are asked to rate the perceived difficulty using a 10-point scale with 0 being the most difficult. The average of the 25 responses determines the overall score for each patient.

At baseline, the average score was 4.4 for the intervention group and 4.9 for controls. At 1 year, the investigation group improved to 7.0, indicating that it was easier to perform daily tasks. The control group scores basically remained unchanged. The difference showed a nominal p-value of 0.001. A similar improvement from baseline to Year 1 was seen in the control intervention group post-treatment.

In summary, the results from our Phase III study demonstrate that bilateral subretinal injection of voretigene is an effective treatment option for patients suffering from vision loss due to RPE65 mutation-associated retinal dystrophy.

The pre-specified primary endpoint was met, demonstrating significant improvement in functional vision.

Voretigene administration also led to statistically significant improvements in visual function, as measured by FST. Improvements were also observed in Goldmann visual field exams. Similar results were seen in the control intervention patients, and the benefits observed at Year 1 in the original intervention group were maintained for up to 3 years following administration, suggesting a durable response.

Overall, the available clinical efficacy data support a consistent, clinically meaningful, and durable treatment effect of voretigene in patients with vision loss to confirmed biallelic RPE65 mutations.

Thank you, and I'd like to turn the presentation over now to Dr. Kelly.

DR. BYRNE: Thanks very much.

DR. KELLY: Good morning. I'm Debbie Kelly, Head of Pharmacovigilance at Spark. Today, I'll present the safety data from our clinical program.

Overall, a single administration of voretigene via subretinal injection in each eye demonstrated a safety profile consistent with vitrectomy and a subretinal injection procedure.

The safety profile includes data from patients followed for up to 9 years, and we will implement a risk management plan

to support appropriate administration and to collect long-term safety data.

The clinical development program included 41 patients in whom 81 eyes received voretigene via subretinal injection. Our Phase I program included 12 patients with 23 injected eyes. In Study 101, a dose-escalation study, 12 patients received administration in a single eye, including 3 patients at the proposed dose. In Study 102, 11 of these 12 patients received the proposed dose in the contralateral eye. One patient did not meet eligibility criteria for administration in the contralateral eye.

In the Phase III study, 29 patients received bilateral injections of the proposed dose, 7 to 14 days apart. In total, 72 eyes were administered the proposed dose.

All patients in the clinical program have been enrolled in a long-term follow-up study for 15 years after vector administration. To date, there have been no patients lost to follow-up.

Phase I data includes patients followed for up to 9 years and Phase III data up to 4 years. With long-term follow-up of 7 to 9 years for Phase I and 2 to 4 years for Phase III, all patients have experienced at least one adverse event.

Most adverse events were mild or moderate, with about 15% reported as severe. Five patients in Phase I and four patients in Phase III experienced serious adverse events during the

extended time collection period. There were two ocular serious adverse events.

Eleven patients in Phase I and 19 patients in Phase III reported ocular adverse events. The majority resolved with minimal or no intervention and without sequelae. All ocular adverse events were analyzed as adverse events of special interest, which I will discuss later in the presentation.

Next, let me review serious adverse events in more detail. During the 7 to 9 years of following patients from Phase I studies, there were five reports of SAEs. The preferred terms are listed here. No events were reported as related.

I'd like to present the details of the ocular SAE of increased intraocular pressure. This event was reported 151 days post-administration and was assessed to be an adverse reaction to a periocular steroid injection. This patient from Study 102 presented with signs and symptoms suggestive of endophthalmitis after the administration procedure.

The patient was treated with intraocular anti-infectives and a periocular steroid injection. The vitreous culture was positive for *Staph epidermidis*, and the event resolved.

Starting at approximately 3 months after vector administration, the intraocular pressure in the eye was persistently elevated above 30 mmHg. The SAE of intraocular pressure increased, and an adverse event of optic atrophy were reported later at about 5 months.

Over the 2 to 4 years of following patients from the Phase III study, there were six SAEs. One patient with a pre-existing medical condition of complex seizure disorder reported convulsion and also reported an adverse drug reaction to an anti-seizure medication.

Another patient reported an adverse drug reaction to anesthesia for oral surgery.

I'd like to review the ocular SAE of retinal disorder. This event was determined to be related to the administration procedure. Loss of fovea function reported 34 days after vector administration. There was a thinning of the central retina and a clinically meaningful loss in visual acuity that did not resolve by 1 year.

To fully understand the potential risks of voretigene treatment, we also analyzed adverse events of special interest across the entire safety population. All ocular adverse events were identified as adverse events of special interest. I'll review the events shown here, as these were identified as important risks because they were assessed as related, with a potential to impact the benefit-risk profile and required clinical management.

Across the program, adverse events categorized as macular disorders were reported in nine eyes in seven patients. These included events of macular hole, macular degeneration, eye disorder, maculopathy, and retinal disorder. One event of

retinal disorder was an SAE and was reviewed earlier.

Four of the events were unresolved at the time data cutoff, one macular hole and the three maculopathy events. Three events resolved with sequelae, and two events resolved. All were considered related to the procedure.

Of the 81 injected eyes, 10 reported an event of elevated intraocular pressure. These occurred in eight different patients. One event of increased intraocular pressure from Phase I was an SAE and was reviewed earlier. All related events were mild or moderate, and most events were transient and resolved without sequelae. Most events were considered related to the administration procedure.

Four retinal tears were reported in one eye each, in one Phase I patient and three Phase III patients. The retinal tears were observed and repaired by the surgeon with laser retinopexy during the vector administration procedures. All events were non-serious, resolved without sequelae, and were considered related to the administration procedure.

With regards to intraocular infection and/or inflammation, 5 of 81 eyes reported events occurring in 3 of 41 patients. These events included one event of culture-positive endophthalmitis, as described earlier. All events were considered non-serious, related to the administration procedure, and all have resolved.

Cataract was reported in nine patients in the clinical

program. Of note, patients with IRDs have a higher incidence of cataract formation than the general population. Additionally, vitrectomy, which is part of the voretigene administration procedure, is associated with a high incidence of cataract formation and/or progression.

Elective cataract extraction procedures have been performed for seven of the sixteen events. Overall, there are nine eyes in five patients with ongoing events of cataract.

In addition to these identified adverse event risks, let me review another safety assessment, retinal thickness. Optical coherence tomography imaging, including central retinal thickness, was collected as a safety measure in the Phase III study.

The mean foveal thickness at baseline was 185.2 µm. Thinning of the central retina was noted in the postoperative period, with a mean change from baseline in foveal thickness at Day 30 of -24.4 µm. This returned to pretreatment thickness by 1 year post-administration.

In summary, the safety profile of voretigene is consistent with vitrectomy and the subretinal injection procedure. Most ocular adverse events tended to occur early and resolve over time, with minimal to no intervention. Many were known complications of intraocular surgery, and most occurred during the first year of follow-up without sequelae.

There were two ocular SAEs reported, and both led to loss

of visual acuity. One was related to the administration procedure, and one was a known adverse reaction to a concomitant medication.

We are proposing a risk management plan that balances the need for further safety data collection while allowing access for this very rare and life-limiting disorder.

First, we plan to limit the distribution of voretigene through approximately five to eight Centers of Excellence in the United States that are associated with an active ophthalmology practice treating patients with IRDs.

Furthermore, voretigene will only be supplied if health care professionals have completed the training program. For the surgical staff, there will be a training program on subretinal delivery of the product, including an in-person workshop with the principal investigators from the program, with a multi-media presentation and wet-lab hands-on training.

Additionally, there will be a detailed surgical manual with illustrations describing the subretinal injection procedure.

There will also be an in-person training program for pharmacists and other pharmacy personnel regarding the preparation of the product. This will include a manual with step-by-step written instructions and illustrations as provided with the submitted labeling materials.

Turning to our other risk management activities, we

continue to monitor long-term safety of voretigene and the administration procedure as part of our ongoing follow-up study. All patients from Phase I and Phase III are currently enrolled and will be followed for 15 years post vector administration.

Safety assessments include annual history, physical and ophthalmic examinations, and clinical labs. Efficacy assessments include most of the measures included in our Phase III study.

Additionally, we plan to implement a prospective observational safety registry to collect long-term safety data from all patients treated in the first 5 years. We will monitor these patients for 5 years post-treatment and collect and assess related ocular adverse events and those potentially related to gene therapy.

Thank you, and now I will turn the lectern over to Dr. Albert Maguire.

DR. BYRNE: Thanks very much.

DR. MAGUIRE: Thank you. I'm Al Maguire from the Children's Hospital of Philadelphia and the Scheie Eye Institute at the University of Pennsylvania. I was the principal investigator at CHOP for both the Phase I and Phase III voretigene studies, and I am here to provide my perspective on the benefit-risk profile for voretigene neparvovec.

First, it's important to keep in mind that nearly all

patients with RPE65 mutation-associated retinal dystrophy will eventually progress to complete blindness that cannot be corrected by optical aids or medical intervention. Other than voretigene, there are no available treatments that can slow or stop the insidious loss of vision in these patients. Currently, their only option is Argus II, a retinal prosthesis approved for completely blind individuals with end-stage RP.

While complete blindness represents the extreme end of progression in RPE65 disease, these patients begin to experience serious manifestations during early childhood. What I see as a clinician are people who are tentative, who cling to their family and friends, and are never without their canes. They can only see in bright light, and they avoid going out later in the day as if they are under a curfew.

These manifestations are exacerbated throughout adulthood as their vision worsens. Until now, these patients and their families could only tolerate their poor vision as it slowly and inexorably deteriorates.

The clinical development program for voretigene established a clear benefit, with 93% of patients showing improvement on the MLMT. What I saw in the clinic was remarkable. Most patients became surer of themselves, whisked aside their guides, and explored their environment independently and with confidence. Rarely did I see a cane after treatment.

In my experience, all changes, including a one-level light change, are meaningful and provide patients the opportunity to gain or regain activities of daily living. Keep in mind that all untreated patients, at best, will eventually get worse and go blind.

When looking at the full-field light sensitivity results, patients on average experienced more than 100-fold improvement consistent with increased rod photoreceptor activity. Now, imagine how difficult it would be to function if I dimmed the lights in this room to 1/100th what they are now. That's what it's like for these patients before treatment.

In most cases, patients noted an improvement just days after surgery. The change in visual field was dramatic as well. An increase of 300 degrees opens up a huge area of vision that was previously choked off by the disease.

The improvements in visual function -- in functional vision were not only prompt but durable. I've seen the improvements in nearly all my patients out to 3 years.

Here I'm showing a video of a young girl before and after treatment. She received voretigene back when she was 6 years old. I saw her in follow-up just last week, and she is now 10. And she cannot remember how poor her vision was back then.

Take a look at the left screen. She now finds it hard to believe that she ever failed this mobility test. And on the right screen, you can clearly see a significant improvement.

And even today, 4 years later, that is how she performs the test.

Next, I'd like to discuss our experience with voretigene delivery. From a procedural standpoint, by age 3, eyes are about 90% of adult size and are at no increased risk for surgical intervention.

Specifically, with the voretigene procedure, we successfully delivered vector in all cases. This includes five surgeons at two clinical sites. No cases of retinotomy site complications occurred during the program. One intraoperative foveal dehiscence was observed but resolved within the early postoperative period without any functional sequelae.

During the Phase III program, all patients were done on an outpatient -- all procedures were done on an outpatient basis, and the average operative time was around 1 hour, which is less time than it took to obtain an informed consent for the study.

Voretigene has a favorable safety profile based on up to 9 years of post-administration follow-up in Phase I clinical development patients. This is a gene therapy where subretinal injection is performed once in each eye, and as expected with a single exposure, most adverse events will occur early and resolve soon after treatment.

Since no additional treatment is needed, there is no repeat risk related to exposure to the procedure or the vector. However, there are some risks to communicate to patients. A

few patients did experience a modest decrease of central visual acuity, even when other tests of visual function improved. And in a few cases, this acuity decrease was symptomatic.

Most of the adverse events reported were related to the surgical procedure. In an effort to minimize surgery-related AEs, we developed a standardized administration procedure that addresses safety findings. Let me walk you through the technique.

First, the surgeon does a pars plana vitrectomy, a standard retinal surgery which is the most commonly performed procedure done by retina specialists. Next, the surgeon selects the injection site, which is a minimum of 2 mm from the macular center. The surgeon then injects voretigene into the subretinal space.

The surgeon will then perform a fluid air exchange to remove any excess voretigene from the vitreous cavity and to limit any exposure to the anterior ocular structures. No special equipment is required, and all the instrumentation is currently available and used for other types of retinal surgery.

The risk of surgical complications have been minimized by using techniques that are already familiar to vitreoretinal surgeons. This includes standard vitrectomy and commonly used instrumentation. The only feature that may be less familiar to some surgeons would be the subretinal injection maneuver. This

aspect will be addressed with mandatory wet-lab training and has been made part of the Sponsor's risk management program.

So, to summarize, there is no available treatment to either improve or arrest the loss of functional vision and visual function in these patients. This is an incurable disease. These patients are visually disabled and without treatment. They will get worse and eventually go blind.

Voretigene provides a clinically meaningful improvement in functional vision, which is prompt and durable, regardless of the extent of disease at diagnosis. Importantly, the safety profile of voretigene is manageable. And in all honesty, if either myself or my child had this condition, I would not hesitate for a moment getting treatment with voretigene.

Thank you.

DR. BYRNE: Thanks very much, Dr. Maguire.

So we're going to move on now to the FDA presentation. We're a little bit ahead of time, but we'll use that during the break possibly. And I want to welcome Yao-Yao Zhu to speak on behalf of the Office of Advanced Therapeutics regarding this biological licensing application.

DR. ZHU: Good morning. My name is Yao-Yao Zhu. I'm the FDA clinical reviewer for this biologics license application.

As discussed by the Applicant, voretigene neparvovec is a recombinant AAV2 vector expressing the gene for human RPE65 protein indicated for the treatment of patients with vision

loss due to confirmed biallelic RPE65 gene mutated-associated retinal dystrophy. I will briefly provide some background information followed by discussion of the Phase I and the Phase III study designs and the efficacy and safety results.

As described by the Applicant, this figure illustrates the critical role of RPE65 protein in regenerating 11-cis retinal in the visual cycle. Next slide, please.

RPE65 gene mutations lead to a deficiency of RPE65 protein and result in the inability to regenerate 11-cis retinal and ultimately retinal cell degeneration and death. Different RPE65 gene mutations can present with a variety of phenotypes. The two most common phenotypic presentations are Leber congenital amaurosis Type 2, in short LCA2, and some forms of retinitis pigmentosa.

The clinical symptoms range from early blindness to progressive visual field loss and ultimately blindness. The prevalence of LCA2 is approximately 1 in 1 million, which accounts for less than 1% of all retinal dystrophies. There is no approved pharmacologic treatment for the intended patient population.

As shown, this is the structure of the viral vector designed to deliver a normal copy of the gene for the human RPE65 protein in RPE cells.

Phase I study incorporated two clinical protocols, Study 101 and Study 102. Study 101 was an open-label, dose-

escalation safety study. In this study, 12 subjects received subretinal injection of the product to one eye, which was the first treated eye. The first treated eye was generally the eye with the worse vision.

Three doses were evaluated. As no significant toxicity was noted with any of the doses, the Applicant chose to use the highest dose for Study 102 and the Phase III study.

In Study 102, 11 of the 12 subjects from Study 101 were administered the product in a contralateral eye or the second treated eye. The treatment interval between the two eyes ranged from 1.7 to 4.6 years.

To be enrolled to the study, the subjects had to be 8 years of age or older, with a clinical diagnosis of LCA2 with a confirmed RPE65 mutation by a CLIA-certified molecular diagnosis laboratory. CLIA is the abbreviation of Clinical Laboratory Improvement Amendments. Under these amendments, the government agencies, including CMS, CDC, and FDA, all have roles in the regulation of the CLIA labs.

These subjects has to have visual acuity no better than 20/160, or visual field less than 20 degrees, sufficient viable retinal cells, defined as retinal thickness more than 100 µm, measured by optic coherence tomography, or OCT, and antibody titer to AAV2 no greater than 1:1000.

Voretigene neparvovec was administered via subretinal injection. Due to a concern of a potential immune response to

viral vector capsid and RPE65 protein, the subjects also received concomitant corticosteroids. Safety was evaluated by adverse event assessment, physical examination, including ophthalmic evaluation, vector shedding, immune reactions, and routine laboratory tests.

The preliminary efficacy was assessed by visual acuity, visual field, electroretinogram, full-field light sensitivity threshold, pupillary light response, and mobility testing.

The study duration for both studies, 101 and 102, was 1 year, with a planned long-term follow-up for 15 years.

The Phase III study included two parts, 301 and 302, and was conducted at two study sites. Study 301 was an open-label standard-of-care controlled trial with a randomization ratio of 2:1 to treatment and control groups.

Subjects in the treatment group were administered the product via subretinal injection to each eye with a treatment interval of 6 to 18 days. Subjects in the control group did not receive the product or concomitant corticosteroids.

In Study 302, subjects in the control group from Study 301 were crossed over to receive voretigene neparvovec in both eyes, with a treatment interval of 6 to 18 days.

To be enrolled to the study, subjects had to be at least 3 years of age, a younger age than for the Phase I study, with a diagnosis LCA2 due to RPE65 mutations, with a visual field worse than 20/60, which is a better visual field threshold than

in the Phase I study, and/or visual field less than 20 degrees in any of the 24 meridians.

Subjects have to be able to perform multi-luminance mobility test, MLMT, the primary endpoint, but unable to pass the test at the lowest light level to allow a minimum margin for improvement. And the subjects had to have viable retinal cells as assessed by OCT.

This diagram illustrates the Phase III study design. In both Study 301 and 302, subjects received voretigene neparvovec at Day 0 and are followed by safety and efficacy assessments at Days 30, 90, 180, and 1 year. As shown by the red arrow, the primary efficacy endpoint was assessed at 1 year after the product administration.

Subjects in the control group received the same assessment at four time points during the first year, and then they were crossed over to receive the investigational product. All subjects were to be followed for a total of 15 years.

As described by the Applicant, the product was administered via subretinal injection, as shown in this figure. To suppress potential immune response, oral prednisone was given at a 1 mg/kg per day, with a maximum dose of 40 mg daily, starting 3 days prior to injection of each eye and then lasting for a total of 7 days, and was gradually tapered off. Next slide, please.

The key efficacy assessments included the MLMT, using each

eye and using both eyes, full-field light sensitivity threshold testing in each eye. FST is a subjective physiological test of retinal function. It assesses light sensitivity of the entire retina by measuring the perception of different light levels, visual acuity testing of each eye.

Safety assessments included adverse event recording, routine physical examination and ophthalmic evaluation, immune responses to viral vector and the RPE65 protein, vector shedding, and routine laboratory tests.

As described by the Applicant, this is an example of the 12 randomized navigation courses designed with the same number of arrows, turns, and obstacles to test the speed and accuracy of the mobility. The MLMT is conducted under seven light levels, as shown at the bottom diagram. Next slide, please.

Each light level is given a score code for endpoint calculation as shown in the bottom row, from 0 to 6. The highest score reflects a better mobility performance under lower light level. Score -1 is given to subjects who cannot pass MLMT at a light level of 400 lux.

The MLMT score was then determined by the lowest light level at which the subject was able to successfully navigate the course. The MLMT score change was defined as the difference between the score at baseline and the score at a follow-up visit, for primary endpoint, the difference between the score at baseline and the score at 1 year.

The primary efficacy endpoint for the Phase III study was defined and in protocol as MLMT score change using both eyes from baseline to 1 year after product administration.

The secondary endpoints were defined in a protocol as following measurements from baseline to 1 year: average change, both eyes, in full-field light sensitivity threshold, using white light; FST; MLMT score change using the first treated eye; average change of visual acuity of both eyes.

Now moving on to efficacy results, the primary efficacy analysis was based on the ITT population, or the intent-to-treat population, defined as all randomized subjects. The ITT population included 31 subjects. Twenty-one were randomized to the treatment group and 10 to the control group.

Two subjects discontinued before intervention, one from the treatment group, due to a severe retinal atrophy, one from the control group, who withdrew consent.

The mITT population, or the modified ITT, included 20 subjects in the treatment group and 9 in the control group. The mITT population was used for exploratory analysis for evaluation of visual acuity changes.

This table shows the demographics of the ITT population for Study 301. The baseline demographics of the two study groups were approximately balanced, except there were more pediatric subjects in the treatment group. As shown in the last column, the average age of the study subjects was 15

years, ranging from 4 to 44 years of age. Sixty-four percent were pediatric subjects. Almost half of the subjects were no more than 10 years old.

The results of the primary endpoint analysis are shown in this table. The median score change was significantly different between the treatment and control groups at 1 year, favoring the treatment group, either using both eyes together or using the first treated eye.

Navigation through the mobility course using both eyes was representative of a real-world situation. However, its outcome may reflect the performance of the better-seeing eye. In addition, the MLMT using the first treated eye was more reflective of efficacy in a single treated eye.

Given the small sample size of 31 subjects, the median MLMT score change was used to describe the mobility performance. This box plot shows the distribution of the MLMT score change using both eyes at four study visits over 1 year. Each box represents the middle 50% of score change distribution, with an additional 25% above and below, as marked by the vertical dotted line.

The median is represented as the horizontal bar in the middle of the box, and the mean as the dot in the middle of the box. As shown on the left, a median score change of 2 was observed for the treatment group at Day 30, and this effect was sustained over the four time points throughout the 1-year

period as a primary endpoint. In contrast, as shown on the right, a median score change of 0 was observed for the control group for all the follow-up visits.

A similar result is seen when the subjects navigated the course using the first treated eye. This table shows the number and the percentage of subjects, with different magnitudes of score change, using both eyes from baseline to 1 year. As shown, 11 subjects, or 52% of the treatment group had a score change of 2 or more. However, only one subject, or 10% of control group, had a score change of 2. No subject in the control group had a score change greater than 2.

Again, a similar result is seen for the MLMT using each individual eye. As shown, 15 subjects, or 71% of the treatment group, had a score change of 2 or more when using each individual eyes, while no subjects in the control group had a score change of 2 or more.

The swimmer plot shows the multi-luminance mobility test results using both eyes for each individual subject. The open circles are the baseline scores. The closed circles are the 1-year scores. The horizontal lines with arrows represent the magnitude of score change and its direction. Shifting toward the right indicates improvement.

The top section shows the results of the 21 subjects in the treatment group. The bottom section shows the results of the 10 subjects in the control group. Subjects in each group

are chronologically organized by age, with the youngest subject at the top and the oldest subject at the bottom.

As shown by the red lines, 11 out of 21 subjects in the treatment group shifted to the right, with a score change of 2 or more. In contrast, 1 out of 10 subjects in the control group shifted to the right, with a score change of 2.

As shown by the four blue arrows on the far right, 4 out of the 8 subjects who had a score change of 1 in the treatment group may be affected by a ceiling effect because their baseline score of 5 was only one light level below the maximum scale.

A similar result is seen in the swimmer plot when using the first treated eye. As shown by the red lines, 14 out of 21 subjects in the treatment group shifted to the right, with a score change of 2 or more. No subject in the control group had a score change of more than 1.

As shown by the blue oval on the left, three subjects in the treatment group did not show any improvement. At baseline, these subjects could not complete the navigation course at the highest light level of 400 lux with a score of -1.

This box plot shows the MLMT score change for the nine subjects who were crossed over to the treatment group in Study 302. Looking at a box plot on the right, a median score change of 2 is seen at Day 30 and sustained throughout the 1-year period over four time points. Looking at a box plot on the

left, a similar result is seen in the treatment group in Study 301, which was shown previously.

With respect to the secondary efficacy endpoints, we will first look at outcome of visual acuity testing. As shown in this table, there was no significant difference in the mean visual acuity changes, comparing the treatment and the control groups, for either the first or the second treated eyes.

Visual acuity measurement used an ETDRS letter chart, or Early Treatment Diabetic Retinopathy Study letter chart. For comparison and analysis, the ETDRS letter chart is converted to logMAR, logarithm of the minimum angle of resolution. Smaller logMAR values indicate a better visual acuity; 0.1 logMAR corresponds to a five-letter change on the ETDRS chart.

The Holladay method converts all chart visual acuity measurement beyond the largest line of letters into a logMAR scale. An active change represents improvement in visual acuity. Next slide, please.

As shown in our exploratory analysis for visual acuity, there were trends towards improvement, based on the number and the percentage of subjects with visual acuity improvement of logMAR 0.3 in each eye. Improvement of 0.3 logMAR is considered clinically meaningful.

As shown, a visual acuity improvement of logMAR 0.3 occurred in 11 subjects, or 55% of the first treated eyes, and 4 subjects, or 20% of the second treated eyes. However, no

subject in the control group had a visual acuity improvement of logMAR 0.3 in either the first or second treated eyes.

We also explored the possible correlation of visual acuity with the performance in the multi-luminance mobility test. Among 11 subjects who had a MLMT score change of 2 or more, a visual acuity improvement of logMAR 0.3 occurred in seven subjects in the first treated eyes and four subjects in the second treated eyes.

Among the nine subjects who did not have MLMT score change of 2 or more, a visual acuity improvement of logMAR 0.3 occurred in four subjects in the first treated eyes and in no subjects in the second treated eyes.

This table shows the outcome of FST testing at 1 year. As shown, there was a significant difference between the treatment and control groups, favoring the treatment group, in both the first treated eyes and in the second treated eyes. FST improvement was noted at Day 30 and sustained for 1 year.

Moving on to safety results, the safety profile was based on 41 subjects or 81 eyes that received voretigene neparvovec in Phase I and Phase III studies. Our analyses focus on ocular and serious adverse events that are related to the treatment, including the product, the concomitant use of corticosteroids, and the surgical procedure.

Thirty subjects, or 73% of the treated population, experienced ocular adverse events. These adverse events

occurred in 51, or 63%, of the injected eyes. Ocular adverse events in 10% or more subjects included conjunctival hyperemia, increased intraocular pressure, cataract, retinal tear, and eye pain.

Other concerning adverse events included eye inflammation and infection, macular or foveal impairment, such as macular hole, loss of foveal function, fovea dehiscence, and retinal hemorrhage.

This table summarizes the two serious adverse events, or SAEs, that occurred following the subretinal injection of voretigene neparvovec in the Phase I and Phase III studies.

The first SAE occurred in a 21-year-old man in Study 102. He developed severe intraocular infection. His vitreous culture grew *Staphylococcus epidermidis*. This adverse event led to prolonged increased intraocular pressure as a result of the inflammation and the use of corticosteroids.

His clinical course was further complicated by developing glaucoma and a cataract, resulting in subsequent ocular surgeries. He eventually developed irreversible optic atrophy due to sustained increased intraocular pressure.

The second SAE occurred in a 19-year-old woman in Study 302. She had a permanent thinning of the fovea after injection and eventually developed permanent loss of visual acuity in her right eye.

The immune response to AAV capsid and RPE65 protein were

measured during Phase I and Phase III studies at time points including Day 14, 30, 90, and Year 1. There were no significant trends of humoral and T cell immune response to AAV capsids and RPE65 proteins.

Of note, oral prednisone was used before and after the product administration with an attempt to suppress the immune response.

In summary, the primary evidence of efficacy comes from 31 subjects, based on MLMT score change. A significant difference in a median score change was noted between treatment and control groups, favoring the treatment group, when using either both eyes together or the first treated eyes.

A MLMT score change of 2, or improvement of two light levels, was seen at Day 30 and is sustained throughout the 1-year follow-up period, as a primary endpoint. An improvement of two light levels or more occurred in 52% of treatment group, versus 10% in control group, when using both eyes and occurred in 71% versus 0 when using individual eyes.

With respect to key secondary endpoints, although no significant change in visual acuity was found between treatment and control groups, there was a trend towards improvement in our exploratory analysis.

A significant improvement for FST testing was found between treatment and control groups. This finding may reflect bioactivity of the product. However, it's clinical

meaningfulness is not clear.

The safety analysis was based on 41 subjects, or 81 eyes. As shown, the treatment may cause transient or permanent complications, such as increased intraocular pressure, infection, cataract, and retinal defect. In the setting of concomitant corticosteroid use, the extent of immune response to AAV capsid and RPE65 protein was limited.

Thank you very much. That's the end.

DR. BYRNE: Thank you very much, Dr. Zhu.

We have time now for a break, but we have also an opportunity to add a little time to the question section, so I'll ask everyone to be back at quarter to, at 10:45 rather than at 11. So that'll give us a little more time for the question and answer session and, if possible, even allow a little extra time for the Open Public Hearing.

So thanks very much. I'll see you back in a half an hour.

(Off the record at 10:15 a.m.)

(On the record at 10:44 a.m.)

DR. BYRNE: All right. Thank you all very much. We're ready to begin the question and answer session. And we will take questions from the Panel, both for the Applicant and if there are any regarding the Agency's presentation as well. So let me begin and see if anyone on the Panel wants to initiate a question to either the Sponsor or to the FDA.

Yes, go ahead.

DR. ZOVEIN: This is to the FDA.

So I appreciated the swim plots that had the age of the patients listed, and I was just curious whether the control intervention arm was added to those plots, or if they were, where they lay out. So I'm talking about these --

DR. ZHU: Yeah, the swimmer plots, right?

DR. ZOVEIN: Yeah. Yeah.

DR. ZHU: So there's two swim prong. One is using both eyes; another is using one -- first treated eye. So you're talking about both of them?

DR. ZOVEIN: Either/or, whether the control --

DR. ZHU: Okay.

DR. ZOVEIN: -- intervention group was added to those or not, or is this all the primary?

DR. ZHU: Oh, yeah. Those -- all the primary. We didn't show the -- we showed the time course, have the crossover, but we did not show -- because we are focused on the primary endpoint.

DR. ZOVEIN: So can I --

DR. BYRNE: Okay. Thanks. One more question? Go ahead.

DR. ZOVEIN: Can I follow up?

DR. BYRNE: Yeah. While you're --

DR. ZOVEIN: Sorry. So to follow up with that, then for the Applicant, do we have an average age of the -- I know, based on the demographics between control and original

intervention they look the same, but if you looked at greater than 2 score on the MLMT, what the age groups were for that subgroup? Anyone has that information?

DR. BYRNE: Kathy, you want to answer?

DR. HIGH: So yeah, I think that we'll need to get that for you after the break, the average age of all of those who had greater than or equal to two light level improvement.

DR. BYRNE: Okay. Brendan, you have a question? Go ahead.

DR. LEE: Yeah. This is a question for the Applicant.

I was wondering whether there was any attempt to look at genotypes. I know all the mutations were obtained as part of the inclusion and enrollment, but specifically, were there patients who had -- who were either homozygous or compound heterozygous for complete loss of function, no mutations, which may suggest there's loss of protein, so protein status, and whether that was, again, in this admittedly small cohort, correlated any way with, for example, the individuals that did not have any response.

DR. HIGH: So no, there was no correlation with -- here, I'll just show, so we can all see it. There was no correlation of outcome with whether patients were missense mutations, for example, versus nonsense or gene deletions, small deletions or insertions.

We did look at immune responses related to genotype, and

again, there was no correlation with whether people developed positive ELISpot response to RPE65 based on their underlying mutation.

DR. BYRNE: Okay. Robert, you had a question?

DR. MASSOF: Yeah. Was prednisone given to the control group?

DR. HIGH: No. The control group did not receive prednisone in the observation year. They did at crossover.

DR. BYRNE: Okay, great.

Dr. Lai?

DR. LAI: Yes. I have a question for the Sponsor.

During the presentation, we saw that there was retinal or more specifically macular thinning as measured by OCT at Day 30, which then largely recovered by Year 1. The slide that we saw was an aggregate of data from the cohort.

I'm wondering if you can give us a sense of how prevalent macular thinning was. In other words, what percentage of the patient experienced macular thinning? And also if you have any hypothesis on what may have caused this, both the cause and the recovery.

DR. HIGH: Okay. I'm going to ask Dr. Albert Maguire to take on --

DR. MAGUIRE: So most patients, after a subretinal injection that goes in the macular area, will have macular thinning. And most of it is due to a loss of the photoreceptor

outer segments. You saw initially the thickness go down and then come up. And the photoreceptor outer segments will become reconstituted. And with that, they go up, back to near normal.

DR. BYRNE: Well, Al, while you're at the podium, can I ask one question to you about site of administration and the influence of the choice of the site of administration on the functional assays? For example, patients who may have had less favorable sites in the superior retina that would have had the most benefit in your assay, regarding functional vision.

DR. MAGUIRE: So I'll put -- answer that two ways. First, we -- in the Phase I study, we learned that if injected too close to the fovea, there was a higher incidence of a macular hole or macular fistula, which was one of the reasons that we tried to maximize the distance to 2 mm from the fovea.

Secondly, most meaningful vision that you have is your central vision, what you're looking at me with, so we just felt that treating in a far peripheral area would not have as much clinical utility as treating the central retina or near the central retina. So we tried to come near the macula, not necessarily going into the macular if we could avoid it.

DR. BYRNE: Okay, great.

Dr. Wu?

DR. WU: Yes. I have a question for the Applicant regarding the placebo group.

So my question is, how can the placebo -- the placebo

group did not undergo some type of a sham surgery. It doesn't necessarily have to be a needle inject into the retinal space. I mean, it could be just going through the motion of, you know, the surgical prep, and perhaps it may be just have a needle inject into the vitreous body, 0.3 cc so that the patient thinks that he or she got some kind of therapy because, you know, there could be quite a bit of significant placebo effect, comparing patients who undergo the whole surgical procedure versus patients who did not undergo any procedures at all.

DR. HIGH: So let me just say a word or two about that. Because the safety data in Phase I were good, and included in Phase I were children as young as 8 years old, in Phase III we went down to the age of 3. And as you know, for children to be included in clinical trials, there has to be the prospect of direct benefit for the child if there is more than minimal risk.

And so to go to an OR and have anesthesia and so forth is really more than minimal risk. And for that reason, we could not do sham surgery in the study. But we also thought it was important to include the pediatric population in the study. Yeah. Do you have another --

DR. BYRNE: Next, do you have another question related to that?

DR. WU: Yes. So may I follow up by asking, I mean, could it be possible that, on the study for the adult patients, then

you have a sham procedure? Because I think, for the children who have the procedure, I'm just wondering how much effect of the changes for the children is due to the fact that, you know, when you have a 3-year-old kid trying to learn this, I guess, the MLMT test, and by the time the kid is 4 or 5 years old, the kid is probably much older, more mature, so therefore you're going to have positive data because, you know, as the kid grows more mature, you know, he or she will pick up the test much faster.

So I'm wondering, on your study design, if it's possible for you to include a placebo group for the adults maybe but not for the children.

DR. HIGH: Well, let me just say that the best way we had to mitigate learning effect was the inclusion of a control group. And so, you know -- thank you. If you look at the data, the control group did include young children, including children as young as 4.

And yet, over the course of the year, with the opportunity to perform the test a total of -- on a total of at least 5 occasions and typically at least 6 and as many as 12 times each time they were evaluated, you see, even then, the learning effect is quite modest. And that control group did include children.

DR. LAI: Thank you.

DR. BYRNE: Other questions?

Another one, Robert?

DR. MASSOF: On the MLMT, when you collapsed 100 and 150 and 200 and 250, did you actually change the light level? Or were you averaging between those two?

DR. HIGH: So in the earlier mobility test validation study, we had had nine light levels. The way this test was done in Phase III, we went down to seven light levels. And so we did eliminate some of the earlier gradations between 50 and 400 when we went from nine levels to seven levels.

Am I answering your question?

DR. MASSOF: Yeah. I guess, the question is whether or not -- you had 100 and 150, for example, but on -- well, the slide that was just up, you had 125. So were you actually presenting 125 or combining data from --

DR. HIGH: No. We were not combining data in the Phase III study. These are the light levels in Phase III. So there was no 100 and 150 in Phase III.

DR. BYRNE: Okay, thanks.

Go ahead.

DR. HAWKINS: Randy Hawkins. To the investigators, Applicants, congratulations with your 100% follow-up with your patients. That's an achievement.

I'm aware of the risk management plan. My question is, is it -- how much of the adverse ocular events are attributable to the skill, expertise, and training of the surgeon? And I

realize you have a risk management plan in force. What will happen if the drug's approved, in terms of the administration of this product to patients, and how much is related to the skill of the surgeon?

DR. MAGUIRE: So we had five different surgeons at two sites, and we had 100% success rate in delivering vector. And the plan is to have, for one of the Centers for Excellence to have a wet-lab training for the one aspect, which would be less familiar to some surgeons, which would be to do the subretinal injection.

And I could call up one of the surgeons who was at the CHOP center who was a novice at this, and she can give you her experience.

Dr. Haller.

DR. HALLER: Thanks, Al.

I'm Julia Haller. I'm the Ophthalmologist-in-Chief at Wills Eye Hospital. And as you can imagine, it was a thrill for me to back up Al Maguire at the Children's Hospital Center for Surgery.

I was -- I'm an example of someone who had to be brought on board, and it was very straightforward. So I'm a retina surgeon. I scrubbed in on 2 days. The first day, Al did two children and I was there, and then the next day I did the surgery.

These are all standard maneuvers that we do in retinal

surgery, the only difference being that instead of injecting something like tissue plasminogen activator or another fluid underneath the retina, we were injecting the voretigene.

DR. BYRNE: Thanks very much.

Dr. Flotte, you have a question?

DR. FLOTTE: The question for the Applicant.

I notice that in the Phase I trial, there as an exclusion for individuals who had preexisting high titer in AAV2 antibodies, and then that was not present in the Phase III or in the current indication. Did you have any retrospective data? Were there any patients with high titer antibodies in the Phase III, and could you draw any conclusions about a lack of effect of preexisting high-titer antibody?

DR. HIGH: So we did track the pretreatment antibody titer in all the subjects in Phase I. And, in fact, we did not see any differences in results based on the pretreatment antibodies. And that's why we dropped the requirement in Phase III.

DR. BYRNE: Okay. Dr. West.

DR. WEST: Connie West, Belmont, Massachusetts.

For the Applicant, regarding the MLMT and thinking about generalizing this if it were to be approved, what percentage of children can -- of various ages, less than say 6, can complete the MLMT, whether they are normal or visually impaired?

DR. HIGH: Okay. So that's a good question. And let me

say that for Phase III, the lower age limit was 3. But in the event we were not able to identify a 3-year-old who was able to understand the instructions and go through the mobility test, there were 4-year-olds who were able to understand the instructions and go through the mobility test.

DR. WEST: But I was asking specifically for the number of children who were screened and those that could or could not complete the MLMT.

DR. HIGH: Okay. So I will have to get those numbers for you after the break. And we'll total up the number who were under -- what would you like? Under 6?

DR. WEST: Yes. That would be lovely.

DR. HIGH: Okay. Great.

DR. BYRNE: And maybe I can interject, too. Can you say that there was relatively good concordance between MLMT and the FST, so non-volitional test contributed to your understanding of the -- which would enable you to test younger subjects?

DR. HIGH: Yes. I think that that raises an important point and I -- you know, I would like to show you some data around MLMT and FST. So if we can pull up the slide of individuals with a single light level change on the MLMT. Yeah. Okay, great. No. I'm looking for the slide with the single light level MLMT change. It's the error plot. Okay, great.

I just want to go through this because I think it's

helpful. These are the 11 individuals, both in the original intervention group and in the control intervention, i.e., after they crossed over, who had a single light level change. So that's 11 -- as you see on the left there -- 11 out of the 29 individuals in the mITT population had a single light level change.

But what I want to call your attention to is, on the right, you see the FST data for that same group of patients. And what you can see for the seven individuals on the left who essentially had a ceiling effect, you can see paired with that their FST.

And what you see here is that the FST gives you an indication that there really is a biological effect on the rods. That's a log scale in the FST plot on the right. And it essentially extends the dynamic range of the MLMT. And you can see that there is a greater effect than what you can appreciate from the ceiling effect. So that's one point.

And then your point about the correlation between MLMT and FST, if we could maybe pull that slide up. There was, in fact, a correlation. And you can see there, on the x-axis is the MLMT score change, and on the y-axis is the change in FST, where now on this scale, the lower the better, the more sensitive.

And you can see that for the control subjects before they crossed over, you see very little change in the FST, whereas

for the intervention subjects, you can see the correlation between MLMT and FST. And this is just a way of pointing out that the MLMT data are more readily understood if you can pair with them the FST data.

DR. BYRNE: Okay. Dr. Brooks, you have a question.

DR. BROOKS: Brian Brooks. I'm wondering if the Applicant can comment on the incremental benefit obtained by treating the second eye sequentially in patients, versus leaving one eye untreated.

DR. HIGH: Well, I think that the difference in the scores between individuals with one eye treated versus individuals with both eyes treated on MLMT indicates that there is a benefit from treatment of the second eye. These data show the MLMT lux scores by first eye alone. And you can see that there were, I think, four individuals who showed no change. But when both eyes are treated -- let's see if I can get this up -- 93% of the patients, or all but two, manifest an increase.

Oh, so that's -- sorry. That's -- we need the -- yeah. Here we go. Yeah. Do you want to add anything to that? Okay. All right.

DR. MAGUIRE: What I would add to that is, in this disease, you're also gaining visual field. So if I'm trying to cross the street or avoid a bicyclist, and they're on my right side, my right eye is not treated and I don't have that expanded field, I'm at a definite disadvantage.

Like cataract surgery, we usually, if both eyes are affected, we find a benefit if both eyes are treated.

DR. BYRNE: Thanks very much.

Dr. Butterfield.

DR. BUTTERFIELD: Thank you. Lisa Butterfield.

For the Applicant, I have a question about the slope of the decline and the longevity of the benefit in your patients.

So you have the natural history study, and you've shown us efficacy data over 1 and 2 years in detail. In the untreated patients, there does not appear to be a decline over that 1-year period.

So my question is, based on the natural history study you have, at what point would you expect to see a decline? And in the treated patients, now that you have, I think, 8 to 12 that are out, you know, at 5 years and longer, do you have any sense of the impact on the natural decline that would occur over time in the patients versus those that are treated?

DR. HIGH: So what I would like to do with that is, first, let me show you the best durability data that we have, and then I would like to ask Dr. Pennesi to comment on the natural history study. And in particular, you know, we didn't show you all of the data from the natural history study, and the visual field declines occur early.

So, first, I would like to note that we have -- our best data for durability come from our Phase III study. We do have

data out to 4 years now, but that has not all yet been submitted to the Agency. And so I would need to ask if it would be all right for us to show that.

DR. BYRNE: Go right ahead.

DR. HIGH: Okay. So I will show you -- and Dr. Reape, in her presentation, showed data out to 3 years for the first five subjects in the original intervention group.

Here you see, in dark blue, the Year 3 data for all of the 20 subjects in the original intervention group, as well as the 2-year data for the control subjects after they crossed over. And what I would now like to show is the 4-year data. Okay, great.

So for the first four subjects in the original intervention group, we have data on MLMT and FST out to 4 years. I'm showing you the MLMT data. It's steady out to 4 years for those first four subjects, as is the FST data.

So what I would like to do now is ask Dr. Pennesi in. He might want to show the visual field data.

DR. PENNESI: Mark Pennesi. So the formal natural history study was a retrospective study, so that did not include MLMT data. It primarily looked at visual acuity and visual fields. And it was very clear, from that data, that if you looked in each age group, which were approximately a few years each, there was a monotonic decline of both acuity and visual fields.

So, you know, what I would say as a clinician who sees a

lot of these patients, to them, even stability is success. And the fact that we're seeing improvement at all is really amazing. Thank you.

DR. BYRNE: Thanks very much.

Dr. Raasch, you had a question?

DR. RAASCH: Yes. Going to the -- returning to the mobility testing, I believe the mobility testing was preceded by 40 minutes in the dark, to fully dark adapt both eyes. Then the first treated eye was unpatched and ran through the test, starting with a low illuminance, at which they failed, and increasing illuminance until they passed, then switched to the other eye and then switched to the binocular.

So by the time they get to the binocular testing, both eyes have been exposed to higher light levels, so they may not be fully dark adapted when they begin the binocular testing. So I wonder if you can comment on the effect that might have on the binocular testing versus the monocular.

DR. HIGH: Okay. So just to clarify that, I'd like for Dan Chung, Dr. Dan Chung to address that issue.

DR. CHUNG: Dan Chung, Spark Clinical Ophthalmic Lead.

So the way the mobility test was performed, after the 40 minutes of dark adaptation, we would actually unpatch one eye. They would go through a test at one light level. Then we would repatch that, take the patch off the other eye, do it at the same light level but at a different course, and then a third

time with both patches off.

So all three testing light level -- all three testing parameters for the eyes were done at the same light level but different courses.

DR. HIGH: Before the lights were turned up.

DR. CHUNG: Before the lights were turned up.

DR. RAASCH: If I can follow up.

DR. BYRNE: Yeah. Go ahead.

DR. RAASCH: Did the testing always start at the lowest light luminance to make sure they failed and then go up one step at a time?

DR. HIGH: Do you want to answer that?

DR. CHUNG: So yes. They were tested at the lowest light level that they were seen to be failing at and then moved up from there.

DR. BYRNE: Thanks very much.

Dr. Pluhar, you had a question.

DR. PLUHAR: Yes. Liz Pluhar. There -- I actually have two.

One is I'm wondering what the area of the bleb is that you create, relative to the total area of the retina. And then, I'm also wondering if you have -- since somebody stated that there were no failures in delivery of the product, if you have any hypotheses on why you had treatment failures.

DR. MAGUIRE: So we estimate about a fifth of the retina

is treated with the 300 µl. And we felt that was sufficient, because if we were to cover -- basically, that can cover the whole posterior pole of the eye, and analogous to treating in diabetic retinopathy, if you can maintain that healthy functional retina, you essentially can have a good quality of life.

And your second question was?

DR. PLUHAR: So why were there treatment failures?

DR. MAGUIRE: Yeah. The treatment failures may well have been due to the fact of insufficient viable retinal cells at the time of the -- and it wasn't reached by the injection necessarily.

DR. BYRNE: Okay. We have one more question from Dr. Massof, and we'll have to probably end after the three of you ask your questions.

DR. MASSOF: Okay. I have a follow-up question to Dr. Raasch on the MLMT.

When were direct -- indirect ophthalmoscopy from those photos, things like that done in relation to the MLMT test?

DR. HIGH: So -- do you want to take this?

DR. MAGUIRE: Yes. So as to prevent them from being bleached, it was after. So it was days after, usually a few days after.

DR. MASSOF: And the pupil dilation, pupil dilation also?

DR. MAGUIRE: Pupil dilation was after as well.

DR. BYRNE: Okay. Brendan, you have a question?

DR. LEE: So this is in relation to the safety and management plan. So is your proposal to continue with, if implemented, the same sequential day limitation, in terms of first versus -- you know, first versus second eye injection?

And if the answer is yes, given the absence of an immune signal as well as the fact that in the Phase I studies you had a significant duration between the first and the second injection, would it be actually safer to allow the consequences of the first injection to have occurred to then consider a second injection?

DR. HIGH: So what I would say about that is that the administration regimens that we have safety data on are at least 16 -- sorry, at least 6 but no more than 18 days apart, or 1.7 to 4.6 years afterwards. And we don't really have safety data on other intervals. And that's why we believe that it should be used in the fashion where we have safety data.

DR. BYRNE: Dr. Emerson, go ahead.

DR. EMERSON: Geoff Emerson. For the Applicant.

Was there any information in the natural history cohort on full-field light sensitivity and when that might decay in relation to the visual acuity or visual field?

DR. HIGH: So, Dr. Pennesi or Dr. Reape, do you have information about FST in the natural history study?

DR. REAPE: Yes. This was a retrospective chart review,

and it spanned many years, so we had one patient who had visits over a 30-year duration. And as you might imagine, from a retrospective chart review, there was a fair amount of variability or variability in testing and even the tests that were performed from visit to visit.

So that's a long answer to your question. But the short answer is no, we did not have very robust FST data available from the natural history study unfortunately.

DR. BYRNE: Okay, thanks.

Dr. Hawkins.

DR. HAWKINS: Thank you.

So regarding the ocular adverse events again, and a question about the intraocular pressure increase and the cataracts, excluding the one person who had the eye infection, which resulted in a permanent elevation of pressure, did the intraocular pressure and the cataracts in the other patients require treatment long term, or did they resolve spontaneously? And what status of cataracts?

DR. HIGH: I'll ask Dr. Russell to comment on that.

DR. KELLY: Debbie Kelly.

So for the intraocular pressure increased events, they're all resolved at this time. The pressure has resolved. And for the cataract events -- can I have my core slide on cataracts, please?

So some of the patients did have cataracts -- had cataract

extraction procedures, and I just want to show you the numbers. So there -- 16 eyes developed cataracts, and 7 of them have had cataract extraction procedures, so 9 still ongoing. In those ongoing eyes, it's visually insignificant, so some opacification seen in the lens but not causing any visual impairment at this time.

DR. BYRNE: Thanks very much.

Dr. Chiorini, you have the honor of the last question for this session. And we'll have an opportunity to ask more questions after the lunch break during our further discussion. So go ahead.

DR. CHIORINI: Thank you.

I wanted to follow up on Dr. Lee's question regarding the immunogenicity of the vector. In looking specifically at your Phase I study where you -- 101 versus 102, some of the patients in 102 seemed to develop, in the report, low-level ELISpot assay. Can you comment on how, the duration of that, and what low really means biologically?

DR. HIGH: So most of these ELISpots, to both the capsid and to RPE65, were negative. And this slide delineates the few positives that were detected. You can see that an occasional subject had a positive at baseline.

I'm just looking at RPE65 now. Are you more interested in that or in AAV?

DR. CHIORINI: Either.

DR. HIGH: Both? Okay. Okay. So for the AAV capsid, you do see that there is an occasional positive at baseline or immediately after surgery, but then nothing after that. And then for the RPE65, again, an occasional positive at baseline and typically nothing after that, occasional positive immediately after surgery.

So these kinds of transient responses, in my experience around, you know, immune responses to AAV, for example, don't -- you know, are not related to anything clinically.

DR. CHIORINI: Thank you.

DR. BYRNE: Thanks very much. Thanks to the Committee for all their thoughtful questions and the Sponsor for their answers.

So now we have a nice opportunity to hear from the public. I'm going to read verbatim a statement that's necessary before all Open Public Hearings.

Both the Food and Drug Administration 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, the FDA believes that 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 you may have with the Sponsor, its

product, and if known, its direct competitors. For example, this financial information may include payment for travel, lodging, or other expenses in connection with attendance in the meeting. And likewise, the 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 the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

So we have the opportunity to hear from 14 speakers. And I'll just ask you to identify yourself. Laura Manfre is the first.

If you want to come forward. And given the amount of time for the 14 speakers, we'd ask you to be concise, and you have about 4 minutes, and allow all the speakers to have that amount of time. If your time is shorter, you can yield it to one of your colleagues.

MS. MANFRE: Thank you. Good morning. I'm Laura Manfre, Co-founder and President of Sofia Sees Hope, which has paid for my travel here this morning. We are a nonprofit organization that receives grants from many companies, and Spark Therapeutics is one of them.

Sofia Sees Hope, named for my now 14-year-old daughter with LCA, is an advocacy organization representing patients and families with LCA and other rare inherited retinal diseases,

including those affected by blindness caused by the RPE65 genetic mutation.

Founded in 2014, we provide funding for diagnosis and research to treat and cure LCA, and provide outreach and education to families, enabling them to share stories, connect, and hopefully provide a little emotional relief from the isolation and devastation that this rare disease causes.

We hear from families whose children cannot make eye contact with their own parents and the devastating impact that it has on the child and the entire family. We hear from kids who face social and academic challenges that range from bullying and exclusion to being perceived as less intelligent, when the only difference they struggle with is that they cannot see as well as their sighted peers.

Even in the best of circumstances, they are growing up with a tremendous pressure that most of us never had to. They will someday live in a world of complete blindness. The emotional, social, and educational toll of this vision loss at a young age is tremendous.

And while there is certainly an urgency to approve voretigene neparvovec for our children, as we know, the benefits are greater when the retina is healthier. I want to share today how important it is to improve any amount of vision for any amount of time for anyone with RPE65.

To this end, I have a letter here from Tami Morehouse, who

was in the trial conducted at CHOP. Tami was diagnosed with LCA almost 20 years ago. Her first treatment was done in March 2009 at age 44, and her second procedure was done in November 2010 at age 46.

At the time of her trial, she had lost so much vision that there were days where she could only see the brightest of light. Here are some excerpts from Tami's letter that she asked me to share with you this morning.

"After my procedures, I no longer lived in fear. A huge weight was lifted from my shoulders. This became especially true when I began to see much more light, differences in color, movement, and more of everything around me, in general. I was once again able to see such things as the faces of family and friends, some letters on the eye chart, and the beautiful colors of a sunset over Lake Erie.

"One of the most important experiences that I've had since my procedures happened was on my last visit with my dad. When I stopped to see him that day, I knew this would be our last time together as he was terribly ill. Before I left at the end of our visit, I put my arms around him, looked into his tired eyes that I could actually see, and told him how glad I've always been to be his daughter and how much I loved him.

"When I got to the door, I turned and waved goodbye. He raised his hand to give me a small wave and smile. I actually saw him do that, and I knew that he knew I saw him. That is a

wonderful memory that I'm sure my dad took with him when he left and I will carry with me for the rest of my life. I'm so grateful that we were able to share something so wonderful during our last time together. The only regret that I have is that my treatment was not able to be received sooner."

Tami's letter, which was also sent to you directly, is much longer, but that is all I have time to share today. I hope that as you consider approving this therapy, you'll remember Tami's story and that it helps you to understand just how very, very important it is for our disease community to be able to retain or restore any amount of vision for any amount of time.

On behalf of Tami and all of the LCA families that Sofia Sees Hope represents, I want to thank you for your time and thoughtful consideration.

DR. BYRNE: Thanks very much.

And the next speaker is Dr. Eric Pierce.

Just identify your affiliation.

DR. PIERCE: Thank you. Dr. Eric Pierce. I'm the Director of the Ocular Genomics Institute and Inherited Retinal Disorders Clinical Service at the Massachusetts Eye and Ear Infirmary and Harvard Medical School. And the Sponsor did pay -- will pay for my travel here today. At least I hope so.

So first I'd like to voice my support of your approval of RPE65 gene therapy, based on my personal observation of the

responses of subjects treated in the Phase I study, which I participated in as an investigator at Children's Hospital in Philadelphia.

Based in part on the positive responses of the subjects that I observed there, I have emphasized gene therapy and development of gene or genetic therapies for inherited retinal disorders in my current role as Director of the Ocular Genomics Institute because I think these therapies have the potential to have the most benefit for preserving and restoring vision for patients affected by these disorders.

So, for example, my response to the question of are the improvements observed in the MLMT tests clinically significant, is emphatically yes. The stories and anecdotes I heard from subjects treated in the trials that I got to interact with demonstrated that their improvements in vision were clinically as well as -- and visually significant in their daily lives, from the stories of kids who could ride their bicycles around the neighborhood themselves after treatment, to parents being able to see things that they dropped, or see their children participate in sports and other activities.

Second, I'd like to comment on the genetic indication for RPE65 gene therapy. I endorse the indication proposed by the Sponsor of biallelic RPE65-associated retinal dystrophy. As described in the FDA briefing document, this is a Mendelian disease in which mutations in the RPE65 gene are necessary and

sufficient to cause disease.

The therapy under consideration addresses the genetic cause specifically via delivery of the normal RPE65 gene to the retinal pigment epithelium, as you've heard. And I think the indication for treatment should be RPE65-associated retinal degeneration.

To be more specific, I don't think the indication for treatment should include traditional eponyms such as LCA or RP. I base this recommendation on experience gained from testing, genetic testing of thousands of patients with inherited retinal disorders which we have performed in the Ocular Genomics Institute.

In our genetic test, we test the sequences of all known inherited retinal disease genes. And when we do this test, this comprehensive test prospectively, we find patients with mutations in genes that were originally identified to be associated with one disorder, like early onset severe disease LCA, in patients with later onset disease, such as RPE, all the time. And as indicated in the FDA briefing documents, this is true for the RPE65 gene as well.

This should not be surprising, as we're all accustomed, in dealing with other diseases in general, to variations in disease severity.

So, again, I would endorse the use of RPE65-associated retinal degeneration as the indication for this treatment.

Thank you very much.

DR. BYRNE: Thank you.

Okay. Next is Katelyn Corey, who's a study participant.

Welcome.

MS. COREY: I am Katelyn Corey, and I am a subject in the Phase III clinical trial of voretigene neparvovec.

Before I begin my prepared statement, I'd like to preface it with a full disclosure that my travel expenses were provided by Spark Therapeutics. I'm also disclosing that I am a VA research assistant and data analyst, but I'm here in a personal capacity. Nothing I state is the position of the VA. I am here to represent myself and experience with this treatment as a subject in the Phase III clinical trial.

It's October, the beginning of the school year, or at least for all of us in the UC quarter system. And I'm a sophomore, majoring in public health sciences and minoring in statistics.

Unlike my cohort, who are figuring out their interests and planning out their dream careers, I have just realized the jig is up; I'm going blind. This is no surprise since I had been losing my sight my whole life, but now I knew I had reached the inevitable.

At first, vision loss is just small things going. When I could no longer see pencil on paper, I used Sharpie. Text is too small? I got large print books. Having trouble with

colors? Who cares. I wear a uniform. But I don't need to tell you about the natural history of the disease.

Vision loss while in school is like the old Lewis Carroll quote from Alice in Wonderland. "My dear, here we must run as fast as we can, just to stay in place. And if you wish to go anywhere, you must run twice as fast as that."

Spending all this time and energy attempting to adapt to my life with ever dwindling vision did not leave much room to live. I was at the precipice of losing it all. I knew I could eventually adapt to being a blind person, but my passions for math and science may not be realized. And that was devastating.

It would have been one thing if I had lost my vision after completing my education. At least then I would have had the knowledge. But this? This meant that even though I could keep running, I could no longer stay in place but would begin to fall behind.

I gave myself 6 months to find and join a clinical trial. As a family, we had followed the research studies for RPE65, from going to conferences, reading the literature, seeing the videos of others who had actually gained vision. Now it was a necessity for me to choose. And I was willing to fly anywhere to receive treatment.

But that very November, the Phase III clinical trial for voretigene neparvovec opened, and I joined the study. And I

was randomized as a control subject in November of 2012.

After waiting an additional year, when I feared I would no longer qualify for the treatment, I was finally treated with the gene therapy in December of 2013, days before my 21st birthday. And let me just say, that was the best birthday I ever had.

I was well aware of the risks and benefits that this treatment entailed. And I would do it over and over again, because for me, I benefited. Within days of the first surgery, I could see vibrant colors again. I was no longer living in a black-and-white film. I could see the clock tower of Philadelphia City Hall, sculptures, windows and all, at night, when mere days before, I thought it was the moon.

I can walk confidently in dimly lit settings, indoors and outdoors. And then there was the sun. It seems funny to say now, but man, that thing is bright. I can practically feel my pupils contracting, which my owl-like eyes would never do before. And then I could go to a restaurant on my birthday, see the plate, the utensils, glasses, and people at other tables, all by candlelight.

These changes were just the beginning. I could use adaptive technology, the iPhone accessibility apps, zoom features, and more. I was independent and mobile, which I had not been for some time. I may not have gained normal vision, but I gained all of my independence.

I just want you to know that this was significant to me, significant in the way that I live and plan my life. I no longer had the fear of what the next year would take away from me. I went to graduate school and got my master's in science of epidemiology this past June. I finally can live my life the way I want to.

Thank you.

DR. BYRNE: Thanks very much.

Okay, Christopher Corey, please come up.

MR. COREY: My name is Christopher Corey. I am the father of Katelyn Corey, the subject you just heard from.

The Sponsor has generously provided my transportation here today so that I can share with you how my daughter's treatment has impacted her life.

My daughter was diagnosed with having Leber congenital amaurosis at 9 months of age, although symptoms were apparent within days after her birth. Initially evident through profound night blindness, her visual acuity had been decreasing steadily throughout her life.

My daughter was treated in December of 2013 at Children's Hospital of Philadelphia, the first eye treated just before her 21st birthday.

While the acuity was not fully recovered, what was cured here was her isolation, dependence, and unfulfilled potential. I once had a daughter who waited years between play dates. The

portable 600-watt halogen butt lamp we took to places so that she could see comfortably indoors was a bit of a deal-breaker.

The nuances of interaction were challenging for her. She was unable to tell one person from another until they spoke. Thus, I'm sure she came off as aloof, a little bit out of touch. Once in high school, there were boys, but no real girlfriends, no confidantes.

Since the treatment, her social world has expanded. Two years ago, it was a significant event in her life when entering a lecture hall, two different people called to her to have her sit with them. If Katelyn had gotten engaged 3 years ago, I do not know who she would have asked to be bridesmaids. A couple of months ago, she had choices to make.

Prior to the treatment, handheld assistive devices were never very helpful. The cast of her own shadow made printed material too dark to perceive with magnifiers. Large print helped with quality printed material, but faint print, enlarged, is just big, imperceptible print.

We did homework together as a family every night until 11 or 12 or later since about the second grade. Her performance became dependent upon the quality of her accommodations. Eventually, we got a closed-circuit TV, and that helped at home. By the time she was in high school, they were providing final exams audio-recorded on an iPod.

She did well in math when provided with enlarged

materials, but exponents and operators were always hit and miss. When she took the ACT exams, a reader was provided, and she scored in the 100th percentile. Even in college, where the disability services were really very good, we still had lessons over Skype to go over notes, papers she had written, and help her use R for statistics classes.

Now, she works independently, writing IRB submissions, doing data analysis on millions of data records. The direction of dependence has changed. Where once she was dependent upon others for her performance, others now depend upon her.

The examples are innumerable. I regret that I did not record Katelyn in the evening after removing the patch from her first treated eye. In a hotel room, eight floors above the street, illuminated only by ambient light, an environment that we all knew had been total darkness for her, she began to point and name things in the room.

The sound of her voice, the subtle gasp of surprise and excitement when she said, "I can see my shadow," was thrilling. I would understand that maybe the fact that she could distinguish between the black silhouette of her shadow and the gray light of midnight may not seem like a life-changing breakthrough, but being able to detect small differences has made a huge difference in her life.

Let me be plain here. This has been a tremendous, life-altering success. It is my fondest desire that other

families have the same opportunity to make an informed choice about this treatment for their similarly afflicted loved ones.

Thank you for your time.

DR. BYRNE: Thanks very much for your comments.

Can I call up Kristin Smedley from the Curing Retinal Blindness Foundation?

MS. SMEDLEY: I'm a mom. I just make things work.

My name is Kristin Smedley, and I'm the President of the Curing Retinal Blindness Foundation. And while my organization has received funding from multiple companies, including Spark Therapeutics, my foundation's covering my expenses to be here with all of you today.

I'm here to support the approval of this gene therapy. There's a dire need for treatments for the inherited retinal disease community.

Now, let me take you back for a second to the year 2000, or Y2K as we called it back then. Now, there was a lot of hoopla and whatever about that the world was going to end, right? Well, in the year 2000, my world, as I knew it, did end.

In a little exam room in Philadelphia, I held my newborn son as the doctor told me he was blind. My baby couldn't see my face. My baby couldn't see me smile. My baby, Michael, had a rare eye disease. Until that moment, I had never even met a blind person before.

The doctor told me he wouldn't play baseball, and he would never drive. Three years later, that nightmare repeated. My second son, Mitchell, was diagnosed with the same inherited retinal disease. A double dose of darkness.

I actually have a sighted child, too, a daughter, and with Karissa, I've seen what it's like for a baby to recognize her mom's face. I've seen her spot me cheering for her on the soccer and basketball sidelines. Those are things that my boys have never been able to do.

Now, I was one of the lucky moms. I was able to leave my career and sacrifice nearly a million dollars in wages to stay at home and guide my boys. I had to teach them how to look at someone when you talk to them and how to navigate a playground. Early intervention teachers spent over 600 hours teaching me how to teach my boys how to access a world they couldn't see.

Preschool teachers of the visually impaired, or TVIs, spent over 350 hours with my boys to teach them to read and write with Braille and to navigate with that white cane. In their school-age years, the TVIs and mobility instructors have spent over 6,000 hours to help them achieve educational goals as well as do things like learn how to cross streets safely.

My boys have spent hundreds of extra hours in their schools memorizing hallways and practicing exit strategies in case of an emergency.

The cost of special teachers and support staff and

adaptive equipment, nearly a half million dollars just to level the educational playing field for my guys. Now, the harsh reality is that most blind and visually impaired children in this country don't receive a fraction of the resources that my guys do.

And even with the best-case scenario that we have and support and them being gifted and as well as, you know, the luxury of having a sophisticated, energetic, educated mom like me, my guys are facing some harsh statistics. Of the 21 million Americans that are considered blind or visually impaired, nearly 70% are unemployed.

Thirty percent of blind and visually impaired Americans are living below the poverty line. Only 31% will get a high school diploma or GED, and only 14% will get a bachelor's degree or higher. My Michael's looking at colleges right now.

He's top in his class in all honors and advanced placement courses, yet due to his blindness, he only stands a 14% chance of getting that degree? Michael and Mitchell are both leaders in their schools and the community, but due to their blindness, their career choices are limited by what's actually feasible for someone without sight. And honestly, they're at the mercy of employers if they're going to take a chance on them or not.

And probably one of the hardest moments for me as a mom is this time of year. You know, Michael and Mitchell can, they can navigate a large, really large high school campus, but

years ago they had to give up trick-or-treating because they just can't navigate at night. And you know kids, I mean, they want to race from house to house to get all that candy.

My boys are resilient, and some even call them courageous. But blindness sidelines them from lots of things. This treatment has to be approved. It has to be approved so that other diseases like the CRB1 retinal disease that my guys have can follow right behind it. It has to be approved so the millions of patients with the thousands of rare genetic diseases have the door opened for them, too.

I so appreciate your work. Thank you so much for being here today.

DR. BYRNE: Thanks very much for your comments.

So the next speaker is Ashley Carper, who is also a study participant.

MS. CARPER: I've also got my son Cole with me too, so --

So good morning. My name is Ashley Carper. Spark sponsored our trip, but that in no way affects my comments today, so --

I'm the mother of two children, both who have LCA. My youngest child, Cole, is here with me. My daughter, Caroline, could not attend and is watching on the web link. And we'd like to say --

MR. CARPER: Hi, Caroline.

MS. CARPER: Hi, Caroline.

Cole and I are here to speak on behalf of our family and experiences in the trial.

Both kids were diagnosed with LCA in 2006. The doctors told us they would be blind at some point and there was no cure. We've heard that over and over again. Their RPE65 gene mutation was confirmed in 2008. They both had gene therapy in Philadelphia during the summer of 2014 in Phase III.

The years from diagnosis to surgery seemed to be the longest 6 years of my life. We hoped and prayed every day for something that would improve their vision. Cole was 8 and Caroline was 10 at the time of surgery.

The young age of our children, combined with the fact that they still had some sight, was a major component in their incredible surgery results. Our highest expectation for the surgery was just that it would stop the progressive loss of vision. Their vision afterwards was better and is better than we could have ever imagined.

The eye exams, up to 1 year post-surgery, showed improvements. Their vision exams have been stable since then. But the true results are played out every day at our house and in everything they do.

Before surgery, Caroline, our oldest child, was a Braille and large-print reader. She is now able to read regular print and is an avid reader. Cole was a Braille-only reader. He now reads Braille but also can read large print. Before surgery,

he could only print his name with a line as his guide. When writing now, he uses large letters, but just having the ability to write his very difficult math homework is something that's pretty awesome to him. He loves math, so --

These improvements, along with many others, have irrevocably changed their life. During the clinical trial period, Cole and Caroline walked through the maze with the many obstacles and signs. Many times they were redirected because they did not see the object or turn.

After surgery, they were able to navigate the maze in the lowest light level with fewer, if any, missed obstacles. Caroline also wanted me to mention that this is extremely helpful at home when the dog is in the middle of the floor.

(Laughter.)

MS. CARPER: That was her criteria. Before surgery, neither of the kids could see in a dim or dark area, as in a dining room. It was a real challenge, and I think we've addressed that here, too. We had to assist in most aspects of their eating in a dimly lit area.

Now they -- they have some challenges now, but really, they don't -- they need little assistance when we're out eating. The improved navigation in the trial maze in lower light is evidence of this improvement also. Our kids now have much better vision than before surgery. We would enroll them in the trial again, no doubt whatsoever.

We truly never expected this outcome. We can move forward and live life with the vision they have and be completely fulfilled. But it is our strong desire for other visually impaired individuals to have the same visual opportunities as our kids have had.

We feel it is our responsibility as beneficiaries to share our input with you. We've been blessed in many ways and want others to enjoy the same improvement in sight, to read print, to be in awe of our beautiful mountains, which we've had vacations and wonderful things after surgery, you know, just to show the kids the many beautiful things that our country has to offer.

We ride -- they can ride bikes now without our verbal cues, which is huge. They could also see the frown lines on my forehead, which they could not see before.

(Laughter.)

MS. CARPER: They point this out quite often also. So -- Cole had a few things he wanted to talk about and mention, if our time allows, so --

MR. CARPER: I can see better in low light, which is why I did better on the maze for the trial. I can stay out later when my friends are outside playing. And before, I had to go in earlier because I couldn't see. And now I feel like part of the group. My vision is not perfect, but what I do have is still very important to me.

I thank you for your time and for listening, and I hope that you will approve this trial so that other kids who need it can have the surgery.

MS. CARPER: Thank you for your time.

DR. BYRNE: Ashley, Cole, and Caroline, thank you for your comments.

So Dr. Eugene de Juan from the Department of Ophthalmology at UCSF is going to make a comment.

DR. DE JUAN: Thank you. The company offered to support me, this travel, but I refused just as, to emphasize the feeling I have about these comments.

I'm a Distinguished Professor at UCSF. I spent 30 years taking care of patients with severe retinal disease. The absolute most difficult or distressing is taking care of a child going blind, dealing with the, you know, the distress of the mothers, the fathers, the families.

I've developed multiple retinal therapies, including participating in the development of the retinal prosthesis, performed over 5,000 vitreoretinal procedures, and was co-director of the retina -- Vitreoretinal Department at Johns Hopkins. I've trained over a hundred fellows. I've performed over 600 subretinal injections for various procedures.

I believe the injection, the procedure of 0.3 mm in a paramacular location is entirely within the skill of an adequately trained vitreoretinal surgeon. The complications in

this trial are not unexpected and were largely addressed at the time of the procedure. As with all surgical procedures as well, all manual tasks, this is, in fact, likely to improve.

To me, these results are extremely impressive. And if my child or my patient or myself had this, I would certainly advocate strongly for it.

Thank you.

DR. BYRNE: Thanks very much.

Misty Lovelace, please come up, who is also a study participant.

MS. LOVELACE: I am Misty Lovelace. My travel has been reimbursed by Spark.

I am one of the -- yeah, well, I can't pronounce it, sorry, in this clinical trial. Without this trial, I have no idea where I would be today. I remember 6 years ago my doctor told me that by the time I was 18 years old, I would be almost or completely blind. That's scary for anyone to imagine.

A year passed, and I found myself struggling to go to school or anywhere that I shall wander. I found myself reading Braille and walking with a cane. My biggest dream was to be normal, to be like everyone else.

When I was accepted for the surgery, it was mind-blowing because I was given a chance to do something about my dream. I wasn't promised that the surgery would fix my eyes or that it would get worse. But to quote Robert Frost, it has made all

the difference.

After having the surgery, I was anxious to remove the patch. The next day, we removed the patch, and I remember opening my eye to the bright, colorful world. Before surgery, my vision was dark. It was like sunglasses over your eyes while looking through this little tunnel.

I remember looking at my stuffed animal for the first time. I did not know you could see hairlines. I remember seeing my mom's face for the first time. One of the best things I have ever seen after surgery was the stars. I never knew that they were little dots that twinkled. However, I honestly say that rainbows are overrated by far.

(Laughter.)

MS. LOVELACE: You may be thinking, would I recommend the surgery? Yes, I would. Nearly 5 years later, I have a future to live up to. I am planning on a career in auto body, and I now have my own business in horse training. I might even be able to get my license. I can honestly say my biggest dream came true.

When I got my sight -- and I would never give it up for anything. I am truly grateful for today's technology. It was truly a miracle. Thank you.

DR. BYRNE: Thank you very much.

Dr. Leroy from Children's Hospital of Philadelphia.

DR. LEROY: Good morning. I'm an ophthalmologist and

clinical geneticist working in the field of ophthalmic genetics. I'm Chairman and Head of Department of Ophthalmology at Ghent University and Ghent University Hospital in Belgium, where I lead the Ophthalmic Genetics Unit, catering for all Belgian patients with inherited eye disease. But I'm also the Director of the Ophthalmic Genetics Clinics at Children's Hospital of Philadelphia, so I rack up the air miles, and I have no time to spend them.

(Laughter.)

DR. LEROY: I was involved in both the Phase I and Phase III studies with the Philadelphia team, and patients of mine from Belgium were included.

I want to disclose that my travel and lodging was partially paid for Spark Therapeutics from time to time. I'm also a consultant for them, with all consultancy fees going straight towards research in ophthalmic genetics at Ghent University Hospital. I do not personally gain from Spark's activities.

Please allow me to talk briefly about some topics important to all of us. I personally follow about 20 patients with RPE65-related retinal dystrophies on both sides of the Atlantic, some for more than 17 years. Two of them were included in Phase I, the Phase I studies, and four in the Phase III.

All patients with biallelic RPE65 mutations have complete

night blindness from birth, whatever the subtype of retinal dystrophy you want to call them. Thus, the retinal disease has an onset from birth or probably even before that. Their retinas remain fairly intact anatomically until an age of 10 years or beyond. But after the age of 10, generally, retinal degeneration sets in. And complete blindness in adulthood is the eventual outcome in all.

So, ideally, all patients should be treated before they reach the point of retinal degeneration. Seen in that light, treatment should happen from birth, or even prenatally in the ideal world. However, mostly surgical challenges hamper treatment before the age of 3.

As people with RPE65-related retinal dystrophy have a retina that keeps its quality for quite some time, treatment from an age of 3 is definitely acceptable. In addition, all patients with sufficient viable retina, and therefore enough potential benefit, should be able to receive the treatment independent of their age. And age -- an upper age limit for treatment, I think, is therefore not advisable.

To address durability of effective voretigene neparvovec, it's interesting to mention that CH-08, the first child to be treated with ocular gene therapy at age 9, was treated in his right eye 9 years ago and in his left eye 7 years ago. He's a patient of mine.

He mentioned that when he left Philadelphia after the

treatment of his first eye, he could see the city lights when flying out of the city with his treated eye and not with his untreated eye. He said that he could see the iris of his mother and see that it was blue, that there was something like an iris because before that he thought an iris and a pupil were the same and just a black hole.

Unrelated patient, CH-10, who was treated in identical fashion, mentioned that when walking through his town at night after treatment, he could see the white stripes of a crosswalk for the first time so he could see much more where to cross the street.

Nine years down the line, and I've seen them in the last month, their ability to navigate in darker conditions is identical to what it was immediately after treatment.

Considering the small sample size of the study cohorts due to the rarity of RPE65-related disease, the results of these trials have been truly impressive. Most of the effect of the treatment is due to the increase in retinal sensitivity, which was measured and shown on the basis of MLMT, FST, and Goldmann visual fields.

The MLMT represents a new and valuable outcome measure. But when evaluating the value of the MLMT scores, please do not forget that the score represents a very lean part of captured information. A majority of patients ceilinged out at 1 lux level. So no further sensitivity improvements could be

measured. Also, the time to completion of the obstacle course is important information available to you but not captured in the score.

In conclusion, I'd like to say the following things: Voretigene neparvovec is a product which has been in the making for 10 years when you consider the human trials, and more than 20 years if you think about Dr. Jean Bennett's and Albert Maguire's pioneering work that is at the basis of this treatment.

I've been extremely impressed by the unique and thorough sense of quality in trial design and execution of it, the never-ending quest for nothing but the truth about patient safety and efficacy, the cautiousness and the perseverance of the teams at Children's Hospital of Philadelphia, the University of Pennsylvania, and Spark. No stone was left unturned, and the treatment is safe and effective.

Voretigene neparvovec is essential to keep our patients from going blind. And I truly believe it is now ready for market introduction so that it can be finally brought to our patients and they don't go blind.

It should be made available to all patients with biallelic mutations in RPE65, whatever the original clinical name given to the condition. I truly believe we have a chance here today to make history.

Thank you for allowing me to speak.

DR. BYRNE: Thank you.

The next is Dr. Joan O'Brien.

DR. O'BRIEN: My name is Joan O'Brien, and I am the Chairman of the Department of Ophthalmology at the University of Pennsylvania, and I am the Director of the Scheie Eye Institute. I have no financial disclosures or financial conflicts.

When I was recruited to UPenn, one of the main attractions for me was the outstanding accomplishments of Jean Bennett, Al Maguire, and their colleagues in developing gene therapy for inherited blindness. I knew of the many years of work that led to their demonstration in Phase I studies that gene therapy could transform the life of a child dependent on using a blind cane.

After therapy, these children became able to see the faces of their friends and their families and to participate in normal life activities such as riding a bike, playing baseball, and completing their homework unassisted. I have had the rare opportunity to witness blind children gain vision because of the rigorous and sustained research efforts of this team.

You've all seen the Phase III data today, and it continues to be stellar. As a researcher with a background in genetics, ocular pathology, and childhood blindness, what excites me is the potential for this work to revolutionize treatment for numerous blinding diseases that currently have limited

therapeutic options.

At the present time, more than 260 genes are known to cause inherited retinal disease. My prediction is that not only will this work transform the lives of individuals with RPE65 mutations, but it will ultimately transform the lives of individuals, perhaps millions, who are now facing a life of blindness.

I remain a very fortunate frontline observer of these life-transforming research efforts, in awe of these researchers and their daily commitment to making the blind see.

Thank you.

DR. BYRNE: Thanks very much.

Laura Gatt, also a study participant. Thank you.

MS. LAURA GATT: Hello. My name is Laura Gatt, and this is my daughter Angelina. We have no financial stake in this meeting. We drove here from New York yesterday and are missing work and school because this is so important to us. Thank you for this opportunity to show our gratitude and to speak about how this treatment has changed our lives.

Angelina was diagnosed with LCA and classified as legally blind when she was 6 months old. She was unable to see indoors unless the lighting was extremely bright. She could function outdoors on sunny days, but at dusk and on cloudy days, she couldn't see well enough to move around freely.

At night, all she could see was the street lights but

nothing else. She couldn't appreciate the beauty of the snow falling or the stars in the sky.

Angelina received this gene therapy in 2013. Her vision improved by three light levels and is stabilized, so much more than we hoped for. For those who live with this condition, an improvement by even one light level would still make a difference in their quality of life.

This treatment has changed my daughter's life. Before she couldn't see well enough to pick out her own clothes or even find things that dropped on the floor. Things of similar color would blend together, so she would have to feel around for them. She couldn't distinguish where stairs stopped or ended or the curb on a sidewalk, but not anymore.

My daughter also couldn't see food on her plate unless the plate was plain white, and she also needed lighting shining down directly on the plate, including to having the lights on in the room. But now she can see so much better that she can go anywhere she wants to eat, even dimly lit restaurants.

School was difficult for her. Sometimes her classmates would make fun of her because of her disability. She needed a one-on-one aide. She couldn't see the board. On her desk was a slant board to put her work on and a light pointed directly down on the work. She also needed to use a magnifier at times.

All her materials were enlarged and bolded. She couldn't use the school locker, her locker, because she couldn't see the

numbers, so she used a lock with a key, but she couldn't see the keyhole. But at least she could feel around to figure out where the key would go in.

But just a few months after being treated, her vision improved so much that she no longer needed any of those items, or her one-on-one aide, and she can now function independently.

It is our hope that this treatment is approved for the sake of all those who need it and are waiting. Thank you.

MS. ANGELINA GATT: Thank you so much for everybody who contributed into me getting my eye surgery, because without it, I would not be able to do anything that I can do today.

For example, when I was younger, in gym class, I wouldn't be able to participate in anything because I wouldn't be able to see anything that was going on. Now I can do everything that everybody else is doing and have just as much fun as they can.

When I was younger, the only sport that I could really see was soccer because I could see the bright white ball against the dark green grass. But I would never be able to play on cloudy days or when the sun was going down because I would never be able to see. I could only play on bright sunny days.

Going into high school, I went in with so much more confidence because I was able to see so much better. So I wanted to try out for the things that I was interested in. I tried out for soccer, and I got on the varsity soccer team.

But I could see so much better, I wanted to try out for something I've never done before.

So I tried out for cheerleading, and I got on the varsity cheerleading team, which would have never been possible without my surgery because I would never be able to see all the motions in stunts that we have to do.

Even something as simple as just hanging out with my friends was difficult. I couldn't see in arcades, movie theaters, or dimly lit stores in the mall. I was never really able to enjoy anything as much as everybody else could. Even just going over to a friend's house was difficult for me.

I could never really enjoy myself because I could never see them or see what was going on around me because it was not as bright as I really needed it to be. But everything -- I can see everything perfectly fine now, and I'm very happy that I can see so much better.

I hope that this gets approved so that anybody that has a problem like mine, that they could get fixed and they could see just as good as I can now.

Thank you so much.

DR. BYRNE: Thank you both.

Now, Elizabeth and Christian Guardino, please step to the podium.

MS. GUARDINO: Thank you for having us. My name is Elizabeth Guardino, and this is my son, Christian Guardino.

And the Sponsor helped provide our travel cost so that we could be here to share our experience as participants in the clinical trial.

On March 14th, 2000, we were elated by the birth of our firstborn, our son, Christian. We were beaming with love for our boy and just treasured every second with him.

Our hearts were soon filled with fear and uncertainty as we noticed strange movements of his eyes, lack of eye contact. He would stare at only -- at whatever light source was in his presence, including directly at the sun.

After a battery of testing and an insane amount of doctor's visits, an ERG was finally performed, and Christian was diagnosed with the extremely rare inherited retinal disease, Leber's congenital amaurosis. At that time, there was so little known about LCA, so our resources were next to nil. We were, quite frankly, alone in watching our child struggle to navigate his very dark world.

Trying to raise a child with this disease, with such little information, for 12 years, only to learn he would go completely blind, was a blow. However, in 2012, we received confirmation that Christian was RPE65, and he entered the clinical trial for gene therapy. I will now let Christian share the miracle we all witnessed.

MR. GUARDINO: Thanks, Mom. The first 12 years of my life were spent in darkness, which was challenging on many levels.

I had quite a few injuries because of my lack of vision, and it was difficult for me socially to relate sometimes because I could not see people's expressions. I guess I saw mainly outlines of people's features.

I couldn't see if somebody was smiling at me or frowning. It was very awkward in the hallways at school because people would walk up to me and they'd say hello, and I would respond with a questioning "hi" because I couldn't see who was talking to me. And that never went over very well.

I could not get around in restaurants, theaters, or on stage, which is something that is very important because I'm a performer. Any outdoor gatherings like barbecues were okay until dusk; then I couldn't play anymore because I was completely blind. I had to sit with my parents or I had to sit indoors with light.

The decision to have the gene therapy was in hopes to stop the inevitable fact that I would be going blind, but it's done so much more. After receiving my gene therapy, I was able to replicate to my mom what my vision with the -- in the brightest and best day would be like.

We were driving home one night, and it was dark, it was rainy, and there was clouds out. And I was wearing sunglasses. I was experimenting, and I put another pair of my mother's sunglasses on, and I looked over, and I said, Mom, this is what I saw on the best and bright day.

Gene therapy has made my world literally so much brighter. I see things that I've never been able to see before, like stars, snow falling, fireworks, but most importantly, the moon. I'm even able now to walk around freely on stage and perform and not just stand in one spot.

I am now able to go to the movies, which is one of my favorite things to do, and now my social life is better because I can go out at night and hang out with my friends at restaurants and different places.

And I can now see people's facial expressions. I can see all of you people right now.

(Laughter.)

MR. GUARDINO: My sight has remained stable for 4 years now after the gene therapy, and I'm now -- and I know now that if I hadn't gotten the gene therapy, I would have been most likely completely blind by now.

I hope and pray that Luxturna becomes available to others with LCA, and it changed my life, my independence, and my confidence. I will forever be grateful for receiving gene therapy and to the amazing team that made it possible.

Thank you all for letting me share my experience with gene therapy.

DR. BYRNE: Thanks so much, Christian.

Okay. Dr. Christine Kay.

DR. KAY: Hello. My name is Christine Kay, and I'm a

board-certified ophthalmologist and a vitreoretinal surgeon from Gainesville, Florida. I have a particular interest in inherited retinal disease and am concurrently involved in multiple inherited disease clinical trials, including retinal gene therapy trials, as a principal investigator and as a vitreoretinal surgeon.

My travel for today's hearing was reimbursed by the Sponsor; however, I have no other financial relationship with Spark.

My patients with RPE65-associated retinal dystrophy are some of my most profoundly affected patients in my inherited retinal disease clinic. These patients present typically at birth with night blindness, reduced light sensitivity, and loss of visual field, which rapidly progress typically to near total blindness in either adolescence or early adulthood.

However, in light of the Phase III voretigene trial, there is now an opportunity to treat these patients and prevent progression to blindness.

When I counsel my patients regarding gene therapy, one of the first things I discuss with them is safety. As a retinal surgeon who has performed a subretinal injection in another gene therapy trial, I am well aware of the potential risks of this therapy. The reality is there are some risks to any retinal surgery, including retinal tears, cataract development, etc.

I think it is also important to point out today that although the product voretigene that we are discussing is novel and groundbreaking, the surgical delivery of this product requires a routine vitrectomy with a subretinal injection, which are procedures that any well-trained vitreoretinal surgeon would be familiar with.

When we look at the safety data of the Phase III trial, ocular adverse events were mild and expected and predominantly surgical-related. The most common ocular AEs were cataract, retinal tear, inflammation, and elevated IOP, and these events were mild and occurred in a low number of patients. This is an excellent safety profile.

As a physician counseling patients, I would feel extremely comfortable presenting this information to my patients and recommending this treatment.

From an efficacy standpoint, there are a few important points I wanted to make today regarding useful visual function outcome measures in this population of severely visually impaired patients.

Our most historically respected visual outcome measure, visual acuity, may not be as relevant to visual function or as readily measured in this population of patients. Additionally, visual acuity is a measure of cone function, so when a therapy is designed to target RPE cells and most likely restore function to rod cells via its fundamental mechanism, visual

acuity is likely not an ideal outcome measure.

However, as a physician who takes care of these patients, I hope that one of my primary take-home points today is to emphasize that quality of life can absolutely be profoundly, positively impacted by improving one's ability to navigate a room, ability to see light, and ability to have side vision. And the Phase III voretigene trial showed significant improvement in these three measures, as evaluated by the MLMT, the FST, and both Goldmann and Humphrey visual fields.

The primary outcome measure, as we are all aware, was this mobility test, which is a maze that a patient is asked to navigate in differing light conditions. I believe this outcome measure superbly addresses the physiologic question, are we restoring rod photoreceptor function in these patients, as well as the functional question, are we positively improving the ability for these patients with this disease to function visually and to live their lives?

Regarding durability of the therapeutic effect, improvements in the navigational abilities and light sensitivity remain stable for at least 3 years. And although we cannot wait for 20-, 30-year data, I fully suspect that in 20 to 30 years, these patients who would otherwise have been blind will still be seeing, will still be navigating that mobility maze as well as navigating their lives as sighted individuals.

I also think it worth reminding us all here today that these patients have no other option. Without treatment, they will invariably progress to blindness.

I have followed this Phase III trial quite closely, and I am convinced of the safety, the durability, and the efficacy of this therapy being evaluated. As a doctor to many patients who have RPE65-associated dystrophy, it is an honor and a priority for me to be here today to present an argument for why voretigene should be FDA approved.

As a mother of three little girls myself, I know how desperate I would be to see this therapy approved if I knew my child were going blind and yet there was treatment available that could stop this and let him or her see.

I will close with one anecdote. One of my patients is a young boy who was too young to participate in the Phase III trial. His mother has become a true friend of mine over the years of us watching him go slowly blind.

He can still see in daytime, but he's almost completely night blind and uses his white cane all the time now. His mother is quite intelligent and motivated and is following the progress of voretigene with piqued interest. She is aware that I am here today speaking to you all.

The child is one of the most upbeat and positive children I know, who doesn't for a second slow down to lament his progressive blindness, although there is no question his vision

loss is progressing, and without therapy, he will soon be completely blind. Mom tells me he runs into everything, even injures himself because he cannot see in most levels of light now.

His response to his disease? A big smile that breaks your heart, and he just says, "My eyes are special." As a physician, I want to be able to treat this child. As a fellow mother, I know how devastating it would be to see my child go blind before my eyes.

As a vitreoretinal surgeon and an academician, it is exciting and historic to be on the brink of seeing the first retinal gene therapy become FDA approved. And I would not be standing here today unless I truly believed this therapy to be both safe and effective and capable of profoundly improving the lives of patients with this disease.

What a life-changing breakthrough it will be if this therapy is FDA approved and we can prevent this child and many others from going blind.

Thank you.

DR. BYRNE: Dr. Kay, thanks very much.

And Dr. Stephen Rose from the Foundation from Fighting Blindness will speak as the last Public Hearing speaker.

DR. ROSE: Thank you. I'm Stephen Rose, the Chief Research Officer of the Foundation Fighting Blindness. I have no financial conflict of interest, nor have nor will receive

reimbursement for being here.

I want to thank the Cell and Gene Therapy Advisory Committee for this opportunity to inform the Advisory Committee about the life-changing results voretigene brings to the individuals affected with Leber's congenital amaurosis 2.

The Foundation was started in 1971 with the mission of finding the preventions, treatments, and cures for anyone diagnosed with a blinding inherited retinal degeneration so that no one would ever be told that they needed to learn Braille, get a cane or a guide dog, and that there was nothing that could be done.

Instead, the Foundation's mission is to support research to preserve and restore sight so that anyone receiving this diagnosis for themselves or a family member will instead hear: "Don't worry, you will not lose your vision; we have a treatment for this."

The Foundation Fighting Blindness has supported the development of this gene therapy from its inception because we believed the potential that this therapy has now realized. Our support started funding the research into RPE65 in 1994, shortly after Dr. Michael Redmond, at the National Eye Institute, identified the RPE65 gene in the eye.

With Foundation funding, the RPE65 gene was linked to the clinical condition Leber's congenital amaurosis (LCA2). And the Foundation Fighting Blindness continued support of the

research to understand how the RPE65 gene could be made into a treatment for LCA2, as well as support for the Phase I, Phase IIA studies at Children's Hospital of Philadelphia.

The establishment of Spark Therapeutics, with funding from the Children's Hospital of Philadelphia, was in part due to the early positive results supported by the Foundation Fighting Blindness.

Currently, there are no FDA-approved therapeutics for inherited retinal disease. Voretigene is the beginning of the realization of the Foundation's mission. The increased functional vision, as clearly shown by the MLMT maze results as a performance-based outcome, the results from this maze show a significant improvement in the functional performance, which was confirmed by the participants themselves in the interviews.

The trial participants reported significant enhanced ability to be mobile in low light, and therefore increased their ability to perform tasks, as you have heard already from some of these individuals in testimony.

As such, this proof of principle, that retinal gene therapy can have a significant positive effect on the progression of retinal degeneration, provides even further reason to be optimistic that other inherited orphan retinal degenerations can be successfully treated using this technology platform.

Not only do we believe this therapy brings a life-changing

benefit to our constituents affected by RPE65 mutations, but it also brings a step forward in recognizing that for people with little or no vision, alternative functional endpoints beyond visual acuity are essential.

The Foundation Fighting Blindness believes the validated MLMT maze presented here is a worthy and relevant endpoint that can measure functional vision gain for our constituents with inherited rare retinal degenerations when there is little remaining vision.

Therefore, we strongly support the MLMT maze as a new and innovative relevant endpoint for our constituents and for this therapy.

In summary, the Foundation Fighting Blindness is excited and pleased to see this milestone achievement toward finding preventions, treatments, and cures. We also applaud the heroes who volunteered to enroll as trial participants, stepping into the unknown for in vivo gene therapy. These people were key to the success before us that has led to the meeting of this Cell and Gene Therapy Advisory Committee.

The Foundation Fighting Blindness strongly encourages the Panel to recommend that the FDA approve voretigene so it can be available for all that could benefit from it.

Thank you.

DR. BYRNE: Thanks very much, Dr. Rose.

On behalf of the whole Advisory Committee, I wanted to

really sincerely thank all the speakers for their insightful comments.

Prabha has a few comments, administrative issues before lunch, but we'll be back in an hour.

DR. ATREYA: I just want to mention for the record that we also have received several written statements from the public in support of this application. And then they were provided -- copies of them are provided to the members around the table in their folders, as well as they are kept at reception -- the registration table in the public viewing binders.

So if you, anybody are interested to look at them, you are free to do that. Thank you.

DR. BYRNE: Okay. We'll reconvene at 1:15.

(Whereupon, at 12:25 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.)

DR. BYRNE: All right. We have the opportunity for more questions and answers, if you all have been inspired by lunch to have any additional questions. We can go through them now.

Yes, Lisa.

DR. BUTTERFIELD: I was hoping to -- question for the Sponsor to have some more detail about the immune response data to both the vector and the transgene and perhaps examples of the ELISpot data with controls to have a better idea about that.

DR. HIGH: Thank you. We did take a look at that over lunch break, and what we're doing now is assembling a slide. And I think it'll be a lot easier if we have the slide. So I'll ask your indulgence for a few minutes about that.

DR. BUTTERFIELD: Thank you so much.

DR. BYRNE: Okay. Other questions?

Yes, Geoff.

DR. EMERSON: Okay. Geoff Emerson here. A question maybe for FDA or maybe for the Sponsor.

The risk management plan, with running a registry and also limiting the procedures to a certain number of Centers for Excellence, is there any requirement to do that, or is that voluntary?

DR. BYRNE: Want to answer from the Agency?

DR. CHAMBERS: Yeah. Wiley Chambers. There is no requirement to do it. As far as what will actually -- at the present time, we're interested in the opinion of the Committee as far as what would be the best avenue, as far as what's needed. But ultimately, the Agency will work out with the Sponsor what we think is in the best interest of patients. But we're certainly interested in hearing recommendations at this point.

DR. BYRNE: Okay. Yes?

DR. HAWKINS: So it's really a corollary question: If the product is approved, what do you anticipate will happen in terms of just the numbers of patients you have to evaluate, the needs, just that sort of a thing, just a feeling about that? I imagine it can get pretty busy.

DR. CHAMBERS: You mean related to implementation of clinical use?

DR. HAWKINS: Yes, correct.

DR. HIGH: So as you saw in Dr. Pennesi's presentation, it's expected that there are perhaps 1,000 to 2,000 patients with biallelic mutations in RPE65 in the United States. There has been much more extensive genotyping of LCA patients, and that's a smaller percentage of the total. And so those are the individuals who would be immediately already identified, whereas there has been less aggressive genotyping of older individuals.

And so it is not expected that there would be, for example, immediately identified somewhere between those 1,000 to 2,000 patients, and it would be a slower ramp-up.

DR. BYRNE: Yes, Brendan.

DR. LEE: Following up on that line of -- to the question, with regards to the inclusion criteria and implementation for OCT analysis and thickness, retinal thickness, do you see that? And is that being proposed as a guideline for who is, would be a candidate for therapy moving forward?

DR. HIGH: So in terms of the clinical trial, there was a, sort of, general guideline of at least greater than 100 µm thickness. Our sense is that if the product is licensed, it should really be a decision of the treating physician.

So if the patient has the confirmed mutations, and they have sufficient viable retinal cells to support the injection, we would expect that IRD specialists would look at the totality of the data and make a determination about subjects who are eligible, rather than having a rigid cutoff of say, FST or VA or -- and, you know, Dr. Pennesi could say a little bit more about that, if he is so inclined.

DR. PENNESI: Mark Pennesi. I agree. I think the important thing is to look at the patient, look at the totality of the data that's available to you, as well as have a discussion about the risk-benefit in an informed consent fashion.

DR. LEE: So though, at the same time, data that you presented all come from that inclusion criteria, and the efficacy is based on at least that, you know, group of patients. So I guess if you're proposing then to take some other totality or measure of, you know, clinical status, I guess, how does that related to the efficacy data?

DR. HIGH: Okay. So Dr. Lee, I will say that we set some inclusion criteria because this was an investigational product. For example, they had to have visual acuity worse than 20/60, people had to have some visual field diminishment as well as the OCT requirement.

We feel that the data from the Phase III trial support the efficacy, and that going forward, it should probably be the decision of the treating physician. I don't know if anybody wants to add anything to that.

DR. BYRNE: So there would be a circumstance which we've seen this develop in other conditions where there may also be an affected sibling who's identified, who's presymptomatic. Theoretically, the product would be available to all of those, that patient community with the appropriate mutation, with the expectation of clinical worsening later.

DR. HIGH: So that's a really good point. But as you know, in our suggested indication, we are saying, reaching an age of at least 3, so that the globe has reached 90% of the adult size.

I don't have to tell all the AAV experts here that this is not an integrating vector and that, you know, if cells are dividing, then, you know, it's going to be lost to the dividing cells.

So I don't know if Dr. Maguire wants to comment on the surgical aspects of under 3.

DR. MAGUIRE: So the concept of 3 years old was devised as a compromise, because we felt that at the age of 3, the eye is surgically anatomically big enough that there is really no increased risk as compared to older patients, adults. Going below 3 years of age, there is an increased risk in amblyopia, and that goes up as age goes down.

There is a narrower pars plana region, so doing a pars plana vitrectomy is difficult. And relative to the rest of the eye, the lens is a bigger size, so causing cataract is again a risk that goes up. And the visual system isn't completely developed, not only the cortical connections to the eyes, but in very young patients, the macula is not yet completely developed till about 6 to 8 months of age.

So it's a compromise risk-benefits. We felt that the risk really jumped at 3 years of age -- below 3 years of age.

DR. BYRNE: Yeah, Brian, go ahead.

DR. BROOKS: Brian Brooks. Also for Dr. Maguire.

On the tail end of that, I have heard anecdotally that in choroideremia, another subject of gene replacement trials, that

the older the patient, the more technically difficult it is to do the surgery in that the surgeons felt that there was more scarring or gliosis that had occurred and therefore that they were at higher rate of having a complication, a surgical complication. What has your experience been with RPE65?

DR. MAGUIRE: So that was a great concern because when you look at the older patients, it does look like when there is intraretinal pigment migration, you wouldn't be able to create a separation. And actually, thanks to Dr. de Juan's suggestions, I've learned that if you inject along the papillomacular bundle, there's always an area thick enough that you can initiate an injection, and usually it spreads quite nicely. So it turned out to be really a non-issue.

DR. BYRNE: Okay. Dr. Flotte.

DR. HIGH: Was -- so Dr. Byrne, before we leave that, can I ask Dr. Russell, who actually had the oldest subject in the Phase III study, to comment?

DR. RUSSELL: Yes. Steve Russell, a PI at the Iowa site.

So I did the two oldest patients in the trial. And in neither of those patients did we have any difficulty creating the bleb. In other conditions, where there is a more extensive chorioretinal scarring, that can be an issue, but for whatever reason, it was not in this particular patient population.

DR. BYRNE: Great. Thank you.

Terry?

DR. FLOTTE: Yes. So I wanted to ask a question of the FDA, kind of on a different track, to move off the surgical points. I'm anticipating, in our next phase we're going to be talking about, a judgment about something being clinically meaningful.

And I've not had experience understanding if there are any precedents or principles that one would apply to something being clinically meaningful for a disorder, a blinding disorder as opposed to a disorder that limits life, you know, that's more life-limiting or cardiopulmonary limiting.

So I wonder if there are any principles that we could be reflecting on relative to the data that we've seen, or is clinical meaningfulness simply, you know, a qualitative judgment?

DR. BRYAN: So clinical meaningfulness is certainly a qualitative judgment, and folks are going to have varying opinions there.

But, Dr. Chambers, would you like to comment on how it's been applied in ophthalmology?

DR. CHAMBERS: Yeah. I agree, it is in the eye of the beholder. There is not a set definition. There are certain parameters that are very commonly used, and we have set benchmarks as far as what is clinically meaningful. Visual acuity is one where we have set a doubling of the visual angle, or halving the visual angle, so 20/20 to 20/40, that type of

amount. It's 0.3 logMAR in this particular case, but we're not talking about visual acuity; we're talking about a different scale.

The common theme that we've tended to use within ophthalmology, and people have heard me say this multiple times, is if I had 20 -- if I had 30 ophthalmologists in a room, and I asked them whether this amount of change was clinically significant, I would expect 28 or 29 of them to say yes.

Those are the types of changes that we say are, absolutely before you run the trial, perfectly fine. And I said something like a doubling the visual angle, I think everybody would say was clinically significant. That doesn't mean that's the only parameter. It means that's a parameter that we would tell you before you ever started the trial, that was clinically significant.

For anything less than that is something that's that clear, we basically look at the benefits versus the risks and do a benefit to risk ratio kind of assessment, and does that meet that kind of test? And that is an individual judgment, and it's one of the reasons why we bring products such as this to an advisory committee to get your opinion.

DR. FLOTTE: If I could ask just a follow-up, does that -- do you specifically talk about activities of daily living in that sort of a formulation, some of which were described by

some of the public testimony?

DR. CHAMBERS: It does. I mean, activities of daily living frequently involve multiple different aspects. To some extent, you can say this maze or pathway that they walk through is a type of visual acuity, because you're following arrows. And if you can't see the arrows, then you -- and, you know, we have eye -- we have visual acuity tests that are an E in different directions. That's the same things as an arrow.

But we have readily said, it is equally important whether you see in bright light or see in dim light. Those are equally important things to be able to fix. So improving the ability to see in dim light, again, the example, I get hit -- I say if I were to get hit when I'm at the side at the road, I care equally important whether it was at dusk or whether it was in bright light. It still hurts just as much. So I want people to be able to see in all aspects.

DR. BYRNE: Constance.

DR. WEST: I was -- for the Applicant, I was glad to see that there was going to be CLIA-certified lab testing, but I did not see the inclusion of a medical geneticist as part of the treatment team. Can you tell me more about that and how you envision that to deal with things that are biallelic RPE65 mutations but that are not disease-causing?

DR. HIGH: So I will note that Spark has a Genetic Diagnostic Group and that we also have, as part of our team

here, a genetic counselor. And perhaps Carmen Trupek (ph.) could comment on availability of genetic counseling services for testing?

DR. WEST: I mean also an M.D., a pediatrician who is specialty trained in medical genetics, in order to help the genetics counselor, who is not a physician -- I wouldn't want a pediatric ophthalmologist doing retina surgery or a retina surgeon doing pediatric eye surgery.

DR. HIGH: Well, Dr. West, at all the Centers of Excellence, the designated Centers of Excellence are all groups that have an active IRD practice.

So I don't know if Dr. Pennesi, you would like to comment on that, or if there's anything else -- but for these inherited retinal dystrophy practices, typically there's a lot of -- people are very conversant with aspects of genetic testing.

DR. PENNESI: Mark Pennesi. So inherited retinal degeneration is not a board-recognized specialty, but I assure you, we're very familiar with these diseases as well as the guidelines for interpretation of different mutations. And those are the guidelines that we would follow.

DR. BYRNE: Other questions?

Sally, go ahead.

DR. HUNSBERGER: Sorry. I was trying to understand, the exclusion criteria, there was one based on retinal thickening; is that right? But there wasn't anything for the MLMT score

because I was just interested that you didn't have anybody in the 0 and 1 category. You had one in the very worst. Is that because you don't think those people could improve, or what was going on there?

DR. HIGH: So the inclusion/exclusion criteria around the MLMT were that you could not be able to pass at 1 lux because then we couldn't measure any --

DR. HUNSBERGER: Right.

DR. HIGH: -- improvement. There were some individuals who with one eye or even both eyes did not get a passing score at 400 lux. So there were some people included in the study who had one or two eyes that didn't pass at 400 lux. And if we can get the slide up of the bilateral -- EE-2, I guess, is that the -- yeah.

So this is -- at baseline, we see for the bilateral testing condition that there is one subject, and she's over there on the right --

DR. HUNSBERGER: Right.

DR. HIGH: -- at age 33 who did not get a passing score at 400 lux.

DR. HUNSBERGER: Right. So just interested in why there -- it just is the luck of the draw who came in? There was -- you don't think it's the retinal thickening exclusion criteria that would have resulted in that?

DR. HIGH: So we don't know how much screening was done

ahead of time by physicians who referred subjects in for evaluation. What I can tell you is that about 80% of the people who presented for inclusion met the inclusion/exclusion criteria. Some people were excluded, I would say, at the young age because -- and somebody asked about this, this morning, so I want to answer that.

Of the -- the trial included nine children 6 and younger. Of all the people who presented 6 and younger, only one was excluded because he could not understand well enough how to execute the MLMT.

And I think he was 3, Dr. Russell, when he presented. And despite the fact that his mother worked with him to try to improve his ability to execute the test, he was not ever able to do it. So 1 out of 10, 6 and under, didn't enroll because of MLMT. But overall, about 80% of the people who presented were able to enroll.

DR. HUNSBERGER: Okay, just another question: So I'm trying to understand the -- I'm a statistician, so trying to understand the biology a little bit more. And so I was -- you were presenting the cycle that it goes through.

DR. HIGH: Right.

DR. HUNSBERGER: Is there a reason -- it seems that most patients kind of max out at a certain step. Is there a reason biologically why that would happen?

DR. HIGH: You mean the number of people who hit a ceiling

effect at 1 lux?

DR. HUNSBERGER: Not the ceiling effect, but it seems like people get to a, you know, a 2, and then they don't improve anymore. Why would that happen? I mean, everybody seems to max out at a certain level, not necessarily the best level. So I was just trying to understand why that might be.

DR. HIGH: Oh, I see. So why are -- why doesn't everyone go to 1 lux?

DR. HUNSBERGER: Exactly.

DR. HIGH: Is that the -- okay.

Do either one of you want to -- you want to address that?

DR. PENNESI: Mark Pennesi. I think it's really an effect of how many viable retinal cells you have left. So there may be an upper limit to how much you can improve, which is why the primary criteria for treatment is evidence of viable retinal cells. And we feel that if you have that, then you should be treated because there is potential benefit.

DR. PLUHAR: So this is kind of a follow-up on that last question. So was there an age effect to the response? So did the children, the younger patients that were treated have more of a response than older patients? And I'm not sure, because maybe they weren't as severely affected when they started. Yeah. They might have just been -- had the ceiling effect there.

DR. HIGH: So this shows the data arranged in order of age

from the 4-year-old on the left up through the 44-year-old on the right. And I would just call your attention to a couple of things. The person with the largest effect on the MLMT was a 20-year-old, and the oldest subject in the trial, a 44-year-old, improved by two light levels. And there were older subjects who went all the way to 1 lux -- old being defined here as 25. And I realize that, you know --

(Laughter.)

DR. HIGH: But anyway, there was improvement across the range of ages. And that's one reason that we really feel that the criteria should be, you know, the genetic diagnosis and sufficient viable retinal cells.

DR. BYRNE: Good. Thanks.

Yes.

DR. ZOVEIN: Hi. I just wanted to also follow up on that. So there seems to be -- you want enough viable retinal cells on the older age range, but the younger, it seems like you also want to leave the window where the proliferation of this population isn't so much that you're diluting out your signal, and since we have to speak to age, so the younger age groups do seem to have -- they all have improvement, but they seem to have less, you know, number of improvement or the MLMT differential. And I'm trying to figure out whether that's due to maybe because they have a 90% size of their adult, so there's a certain population that's proliferating and maybe

diluting out the ability to really capture the terminal population and/or they're also developmentally, from a child development standpoint, a little on the young side to follow these kind of directions.

So is their decreased, sort of, response due to one or both, or do you have a sense of that?

DR. HIGH: So, again, you know, I'm trying to understand your question as clearly as possible. So are you --

DR. ZOVEIN: So, yeah, I guess I'm using the FDA swim plots a little bit more, but generally 3 and above, so if you looked at MLMT of 3 plus, generally that seemed to cohort with, you know, right around age 11 and up, for the -- you know, the majority, if you're looking at the same baseline. Is that --

DR. HIGH: Well, right. I was just going to say, if you look here at the chart, you know, if you look at children, let's say, 8 and under, I mean you probably do have more individuals who began at -- able to pass at 4 lux on the left-hand of the chart as opposed to the right-hand side.

DR. ZOVEIN: Okay.

DR. BYRNE: Yeah.

DR. ZOVEIN: Okay. Because, you know, from the animal data, it seems like there's a 10-year, sort of, beneficial effect, so I guess I was trying to figure out, if you're treating, sort of, on the younger side, will that, you know, possibly 10-year effect be maintained, or are you going to have

a diluted again, a growth of the eye?

And this ceiling effect, you could call it ceiling effect, but then you wonder what, you know, at age 8 or 10, once they have a little bit more child development milestones, whether they're, you know --

DR. MAGUIRE: So the cells are terminally differentiated, essentially by 8 months of age. So it's not a dilutional effect of the vector. So the eye grows, but the number of cells does not increase.

DR. ZOVEIN: So the 90% adult size had to do with surgical, not --

DR. MAGUIRE: Correct. Yeah.

DR. ZOVEIN: Okay. Okay.

DR. BYRNE: One more question.

Michael.

DR. LAI: Yes. So my question is to do with another endpoint that's been discussed this morning, which is visual field. A number of you have talked about improvement in the visual field in treated subjects. And I'm wondering, in your looking at the data, is there any correlation between the visual field improvement area and the injection site? Or -- right. What I'm getting at is, sort of, trying to figure out if there's -- if there is a correlation, then do you see any added benefit in additional administration? Might there be rescue of additional areas of retina?

DR. HIGH: Well, Dr. Lai, I think you're asking a really good question. And I was hoping you were going to ask if there was a correlation between Goldmann visual fields and the multi-luminance mobility test, because there is.

But you're asking about correlation with the injection site, and I don't know if we have those data or even if we could quickly develop them in the back room, because they really require us to go back to the source data, unless either of the operating surgeons feels that they could address that. I mean, I think --

DR. LAI: Well, all the injections are given along the superior vascular arcade. So, in theory, you would see an improvement in the inferior part of the visual field. And if that's the case, you know, maybe we're rescuing a specific area of the retina. And might there be added benefit to additional administration, resulting in rescuing of additional retina?

DR. HIGH: Okay. Well, let me just say first that we don't have data that addresses multiple administrations to the same eye. So I can't comment on the safety of that.

Do you want to address anything about the visual field?

DR. MAGUIRE: So in the Phase I, we did actually look at the correlation, or there is a correlation between the area treated and the area of visual field that's expanded. The thing is the -- I guess one question is, if you take the dose, which is 300 µl, and you inject one area or you break it up

into 100, 100, 100, is the surface area you treated different? Frankly, I don't think it'll be that much different.

So the only way of increasing would be to change the dosing, which I don't think, you know, that our safety data would -- yeah, we have no information on that.

DR. BYRNE: Dr. Pluhar.

DR. PLUHAR: Can you just clarify what you just said? Because I thought I read in one of the Phase I studies that you -- there was no significant difference among the three doses that you examined.

DR. HIGH: That's a correct statement.

DR. MAGUIRE: Yeah.

DR. HIGH: Doses --

DR. MAGUIRE: Here you --

DR. PLUHAR: Maybe it was in different mutations.

DR. HIGH: Yeah. I'm not sure I totally understand the question.

DR. MAGUIRE: So what I would say is that is correct, but the fact is the dose that you deliver doesn't necessarily correlate with the surface area of the bleb that you create.

(Off microphone question.)

DR. BYRNE: Can you turn on your microphone?

DR. PLUHAR: Sorry. I do recognize that the two lower doses were half the volume.

DR. MAGUIRE: Right.

DR. PLUHAR: They were 150 µl rather than 300. But I would -- I guess I would have expected for you to recognize that there was a difference in the response to the doses when I believe what I read was there was no dose-related response.

DR. MAGUIRE: In terms of the visual field?

DR. PLUHAR: I'm not quite sure what you measured in the Phase I, in Study 101.

DR. HIGH: Okay. Let me -- so that's a good question. Let me just say this, that most of our best data on dose escalation comes from animal models, where all the animals have the same mutation and you can inject them at the same age. And then you can clearly discern a dose response.

But in humans who were in the trial, who presented at a lot of different ages, and all with different mutations, unless they were siblings, it's difficult to discern a dose response in the Phase I study.

DR. BYRNE: Yeah. Okay. I think now we have the opportunity to go on to the questions that were posed to us. And Dr. Raasch will address the first question, begin that discussion.

DR. HIGH: Dr. Byrne -- oh, sorry.

DR. BYRNE: Are you ready for the --

DR. HIGH: Was still --

DR. BYRNE: The immunology data is ready?

DR. HIGH: I don't think I have that yet. And I would

therefore like to request that when we do have it --

DR. BYRNE: Sure.

DR. HIGH: -- I could put it up.

DR. BYRNE: We can come back to it.

DR. HIGH: But also, there was one other question that was asked before lunch that I wanted to get back to. And I'm sorry. I can't remember who asked it. But the question was, if you divide the subjects up into those who experience greater than or equal to two light level changes on the MLMT --

DR. BYRNE: Basic age.

DR. HIGH: -- what was the average age of that group --

DR. BYRNE: Right.

DR. HIGH: -- versus the ones who had less than two? So for the original intervention group, for those that had greater than or equal to two light level changes, the average age was 14. For those who had less than two, it was 15.

In the control intervention subjects, so after they crossed over, the average age of those who had greater than or equal to two light level changes was 14, and less than two, it was 16. So those are the data we have on that.

DR. BYRNE: Great. And --

DR. HIGH: And we'll get the immunology data ASAP. Sorry.

DR. BYRNE: Yeah. So if there's no objection, that -- we'll insert that whenever amongst the discussion related to the question.

So, Dr. Raasch, did you want to go ahead regarding Question 1?

We're going to put the questions up so that everyone is familiar.

DR. RAASCH: Okay. So this first discussion question asks us to consider whether or not a two-light level improvement in the MLMT is clinical meaningful.

And I think that we've seen a lot of evidence to show that -- and seen videos, how performance can change pre- and post-treatment. And in everyday life, we experience visual tasks like that, when we're walking around in familiar or unfamiliar environments.

The task itself was fairly compact. It was all done in a 5 by 10 foot space. And so that's a lot smaller than many of the tasks we're asked to deal with. But the visual tasks that drive the performance on that have a lot to do with visual acuity, seeing the arrows against the background, detecting the presence of obstacles.

An important obstacle that was included in this are steps, uneven surfaces, and so forth. That's particularly meaningful for many visually impaired people in navigating and walking around, because not only is it difficult to see steps and curbs sometimes, but the consequences of missing that can be consequential. It could be -- might mean a fall, stumbling off a curb, or something. So I think inclusion of that particular

type of obstacle is valuable.

So while it's -- I don't think it's possible to design one standardized course, even 12 different versions of that course, that entirely reflect the sorts of tasks we encounter when we walk around under different illumination conditions, I think this task -- this test did design -- did achieve to capture some of the important characteristics of -- and to reflect changes in performance.

DR. BYRNE: Okay. So now I'd like to get some discussion from the other panel members, at least regarding this part. So we'll do (a), (b) separately.

So, Terry, do you want to make a comment about clinical meaningfulness?

DR. FLOTTE: Yeah, certainly. I just -- I did have a question, maybe for one of the ophthalmologists in the group.

A secondary endpoint was included in the package, referring to a questionnaire that is described as National Eye Institute VFQ-25, which is an attempt to capture quality of life, activities of daily living. This goes back to the question I asked to the FDA before.

It also -- obviously, we've heard very, what I would consider to be very compelling firsthand description of functional benefits. I just wondered if this -- if other people who have experience in ophthalmic therapeutics have, you know, have used these types of instruments before and whether

you could comment on that.

I know it wasn't their primary endpoint, but it seems to corroborate the MLMT results.

DR. BYRNE: I mean, and maybe while people are thinking of their question, Wilson, you could comment. I mean, this is in keeping with the effort to not only understand how patients function but how they feel as part of the regulatory review.

DR. BRYAN: So we're certainly interested in these outcome measures and trying to sort out or help us sort out what sort of changes are clinically meaningful. But our review is ongoing, and we don't have a particular position on this outcome measure.

We too would be interested in the ophthalmologists on this Committee, if they have any comment.

DR. BYRNE: You want to comment, Robert?

Yeah. This topic.

DR. MASSOF: Discussion Question 1? I have a concern about the step size. What was done was to measure the amount of light on these mats at seven different light levels and then convert those light levels, which are physical measurements, into ordinal scores.

So a two-score change from 50 to 4 is 1.1 log unit change in luminance. A two-score change from 0 to 2 is half a log unit. That's big. So the question is why go to an ordinal scoring system when you've already had physical measurements?

The visual acuity's measured, the log resolution. FST is measured in log illuminance, or log luminance. Why not -- what you're really doing is measuring a threshold for passing the test, which is a dichotomous score, just a 0 or 1. You pass or you fail.

And you could ask, what's the -- in principle, you're trying to find the point where there's a 50% chance of passing, what light level is required. So I don't think you can interpret a two-score change as meaning the same thing, depending on the starting point for that change.

DR. BYRNE: So this is more of a biostatistical question about then, I guess, to the point of meaningfulness, whether the magnitude of the score reflects the physiology, where there might be --

DR. MASSOF: The score doesn't give you the information you want. And the measurement's already made in light units, in luminance, in lux. You convert that to a log scale, you could actually report the outcome in terms of log light level.

DR. FLOTTE: So I don't want to answer the question, but I would just make one countering point, which is that the assay, an assay for the function that was being restored by this gene did not exist, and so they created one. And somebody could have created a different one, but I thought it was very helpful to note that the majority of the patients actually hit the ceiling effect. In other words, they were able to navigate

without -- they were able to pass, I guess, is as you said, dichotomous to the -- the majority, the vast majority, I think, if I remember the percentages, was over --

DR. BYRNE: Yes.

DR. FLOTTE: -- 65% or something, were able to pass at the lowest luminescence tested. So it doesn't seem that under that circumstance -- I mean, your point is very valid in a sense that it's not linear or logarithmic. It's ordinal. But it -- if you look at the data that's there, it seems to indicate that the task would --

DR. BYRNE: Yeah.

DR. FLOTTE: -- it would have scored well under an alternative numerical scale.

DR. MASSOF: Well, I agree that there were impressive effects and big effects. But from a point of view of the validity of the test and the measure that you're using, to convert this to an ordinal scale throws a lot of information away. It makes the score uninterpretable.

So I think that, since you're already working in light units, why not stay in that? I mean, it's -- might just require a reanalysis or representation of the data, not do the study over, but I think the way it is now, the primary outcome is the score change.

DR. FLOTTE: If I could just offer a different interpretation perhaps is that perhaps it -- it does throw a

lot of information away, but perhaps it might not make it uninterpretable with a dramatic difference between the two conditions.

DR. BYRNE: Correct. The effect size is still seen. And maybe if you could comment, Dr. High, really, in the context of our question about clinical meaningfulness, do you feel that you can substantiate the change in performance as is, was measured as you presented?

DR. HIGH: So I want to try to address the question, but I want to make sure that I understand the question. So one thing I can point out is that if you look across the -- I don't know if we -- able to project this.

DR. BYRNE: Slides. We'll switch.

DR. HIGH: If I understand the question correctly, Dr. Massof, are you asking the question about would it have been preferable to make each of the units, let's say 0.5 logs, or some precise exact interval that was maintained throughout the scale?

DR. MASSOF: Well, the analogy would be measuring visual acuity as lines of change. And if you -- if between some lines there's a tenth of a log unit change, other lines it's two-tenths of a log unit change, other lines might be -- but you're just reporting lines of change.

If you just express these as log luminance, then you're in a unit -- you're in a system already where you can interpret it

as a threshold. Now, the problem is that you have a 6/10 log unit change for your first step, 4/10 for the second one, 7/10 for the third, 4/10 for the fourth, 0.25 for the fifth, and 0.25 for the sixth.

So it's a very uneven scale. And depending on where you're operating on that scale, a two-score change means something different.

DR. HIGH: Yes. That -- so I agree with you. I will say that the genesis of the test was to relate to activities of daily living, and that's why the intervals are uneven.

I will also point out that for most of the subjects -- if we can have EE-2, what you see is that for most of the subjects, the activity is concentrated from 50 lux down, where you are right, there is some unevenness there. But the analogous, exact 0.5 log unit steps would have been 1 lux, 3.3 lux, 10 lux, and 33 lux. So it's not precisely half log, but it's close.

DR. MASSOF: No, it's not. And if you look at -- if you have to look at the numbers --

DR. HIGH: Okay.

DR. MASSOF: -- they ran from 0.25 to 0.7 in terms of your log steps. And so --

DR. HIGH: Okay. Can we put up the other candela-per-meter-squared slide? Okay. Does this help or not? No. Okay.

The one we made yesterday?

DR. BYRNE: While they're getting their -- okay. We have another comment.

Go ahead.

DR. JOHNSON: I'm Chris Johnson, a neuroscientist and professor in the Department of Ophthalmology and Visual Science at University of Iowa. And I will, first of all, say I am a staunch believer in continuous functions rather than discrete. But I think there's also a question here that needs to be addressed.

One is does -- do things improve? So that might be more of a bipartite type of thing. Do they get better or worse? And the other issue is how much?

Certainly, we have log candelas-per-meter-squared values for all of these. So that could certainly be recomputed and recalculated and determined in a more sense that would be consistent with the photometric determinations.

So I think that's a good suggestion. And I think that would be useful, to see if that corroborates the ordinal scale.

DR. BYRNE: Okay. Thank you. That helps.

Brian Brooks, question.

DR. BROOKS: Brian Brooks.

From a standpoint of a practicing ophthalmologist who sees patients with inherited retinal degenerations every week, I think that this is a meaningful change. I'm sure that the specifics of the test, of the scale, will mature, be augmented

over time. But I think that increasingly, for patients with very low vision, that looking quantitatively, as quantitatively as we can, at what are activities of daily living is a very important thing. And I think the Sponsor has done a good job of convincing us of that.

DR. BYRNE: Okay, great.

Yes, go ahead, Dr. West.

DR. WEST: I would -- as a fellow pediatric ophthalmologist, to Dr. Brooks, I would echo his sentiments that this is -- it's not a perfect tool yet, but it's way better than what we have with visual fields and high contrast visual acuity.

My concern, as a pediatric ophthalmologist, is that this does not serve a developmentally delayed population, nor does it serve the youngest children who may not be able to qualify because of their young age and ability to cooperate.

Specifically, though, going back to Dr. Maguire's question, the amblyopia could limit the -- if you were able to treat at a very young age, say less than a year, you may have better functional central acuity if you didn't have amblyopia on a cortical basis at the end to deal with.

And so that's something that, under this umbrella, we can't address, but it's something that I would hope the FDA would encourage the Applicant to explore further.

DR. BYRNE: Go ahead, Grace.

DR. PLUHAR: Grace Pluhar. I think I'm getting a little confused because I understand we're discussing the validity of this test to measure function after treatment, but we're not -- one of the criteria for future treatment, or if this is approved, you're not going to have to have a certain MLMT score; is this correct? I mean, that's not going to be something that is going to be used to say you can or cannot be treated?

If you're 2 and you can't do this test, doesn't mean that you can't get treated? Well, I guess 2 is too young because you're limiting the -- so 3. So if you're 3 and you can't actually do this test doesn't mean that you wouldn't be a candidate for treatment; is that correct?

DR. BYRNE: My understanding is that would be correct. If the label advised and the treatment centers used guidelines for their postmarketing commitment, then this would be up to those treating physicians to make that determination about the degree of severity and the potential for benefit.

Marcia.

DR. CARNEY: I just have a question. When you all did the surgery and you put in the subretinal medication, did you take postoperative pictures with regard to the level of area with which the contact to the retinal pigment epithelium the drug comes? And does it in any way look at all like the visual field changes that you may see, say, months down the line, from

that person's improvement?

DR. MAGUIRE: Al Maguire. So we did -- postoperative pictures are not helpful because within 4 to 6 hours after the surgery, the sub -- the bleb reabsorbs. You don't see it the next day, and you don't see any high water mark or any --

DR. CARNEY: No change in the RPE that are going to let you think that that's the edge of where it was so that you could actually measure it via scope?

DR. MAGUIRE: Absolutely correct. We would make --

DR. CARNEY: Okay. That's what you mean.

DR. MAGUIRE: -- pictures, and we had intraoperative videos which showed the areas we injected, indeed, correlated with the visual fields at that point.

DR. CARNEY: I was going to say, and that would actually work with looking at the MLMT and give you some ideas to what you're going to have for improvement in your function.

DR. BYRNE: Other comments regarding this question?

Sorry? Oh, did you also want to make a comment? No? Okay. They're all set.

So, Dr. Raasch, you want to continue with Part (b)? Any other points there?

DR. RAASCH: Well --

DR. BYRNE: We'll put that part up.

DR. RAASCH: Okay. Part (b) asks whether or not, if you consider that a two-light level improvement is not clinically

meaningful, please discuss whether or not a larger change would be clinically meaningful or whether any other endpoint in the clinical trial is clinically meaningful.

So considering Dr. Massof's comments, the two-light level improvement means somewhat different things, depending upon where you're starting. The slide we saw a few slides ago could be easily redrawn, just tweaking the positions of the different light levels to correspond with log luminance or something. But -- and it would adjust the length of those arrows we saw.

So I think we've seen evidence, we've heard evidence that the two-light level improvement, with it, those caveats, is meaningful. It demonstrates -- it helps us see that performance improves in this particular task.

To consider the other endpoints, I was interested in the one secondary endpoint that didn't show a statistically significant difference, and that's the visual acuity. And I was curious about how systematically it was measured. And for example, there was discussion about the use of finger counting and hand motion acuities.

The way it was described, the acuity testing started with the printed chart, the ETDRS chart where the largest letters are a certain size, 40 mm letters, and the shortest test distance was half a meter. Now, that would -- if a patient read that top line and nothing else from half a meter, that would correspond to 20/1600 acuity, or in logMAR terms, 1.9.

So that's getting pretty far down there.

So I'm wondering if the finger counting and the hand motions was used -- how often that was used, and if it was -- if the examiner was free to resort to finger counting whenever they felt like that would be easier or most useful, or if there was a systematic rule for how --

DR. BYRNE: Okay.

DR. RAASCH: -- that acuity testing was carried out.

DR. BYRNE: So a question maybe for Dr. Maguire, Dr. Bennett, or Dr. High.

DR. MAGUIRE: So could you ask the question or rephrase the question?

DR. RAASCH: Yeah. So the question is, using the ETDRS chart from half a meter, the lowest acuity you could measure was 20/1600.

DR. MAGUIRE: Correct.

DR. RAASCH: And was that the threshold for moving on to finger counting at a closer distance or --

DR. MAGUIRE: Yeah. That is correct.

DR. RAASCH: Okay. So it was really just a small proportion of the acuities that were reported that actually were the result of the finger counting?

DR. MAGUIRE: That would be correct.

DR. RAASCH: Okay. So I was curious about that because we can imagine that that sort of acuity measurement is more noisy,

less repeatable, and so forth.

DR. MAGUIRE: Yeah. And in point of fact, that we used the conservative Holladay off-chart measurements, which actually drag down the acuity, because we're using larger -- we're considering a larger interval as opposed to the Lange scale, where in fact, if you apply the Lange scale, which is less conservative, we indeed did see a significant acuity change.

DR. RAASCH: Yeah. So my understanding of the finger counting, though, is that say a hand is about the size of a 200-foot letter. So if you can finger count at 2 feet, that's 2 over 200 essentially.

DR. MAGUIRE: Yeah, correct. And but it's -- you can --

DR. RAASCH: But the Holladay's --

DR. MAGUIRE: Yeah.

DR. RAASCH: -- adjustment relates the finger counting to hand motion. There's a log unit difference there, right?

DR. MAGUIRE: Exactly.

DR. RAASCH: Okay.

DR. MAGUIRE: And the Lange is more -- is less conservative. It's at 0.3 log unit. So --

DR. RAASCH: Right.

DR. MAGUIRE: -- for that reason, you see that with using the Lange scale, indeed, we appear to have a better result than the Holladay scale.

DR. RAASCH: Another question about the acuity measurement, the Holladay paper discusses, sort of, interpolating acuities between the whole line increments, individual letter counting, so forth. It was -- but I didn't see explicitly in the briefing documents whether or not that was done.

DR. HIGH: We did go by letters, not by lines. Is that --

DR. MAGUIRE: Yeah. It was --

DR. RAASCH: Okay.

DR. MAGUIRE: It was the total number of letters. Yeah, it's just like ETDRS. Yeah.

DR. RAASCH: I would -- yeah. Okay.

DR. BYRNE: Maybe you could also comment on the continuous measure of FST because there was observed a 2-log increase in white light sensitivity. That really is a more of a continuous measure, kind of to the point of Part (b) of the question. Any concerns about that? Or is that a valuable, meaningful measure as well?

DR. MASSOF: I think it was a good corroboration of what was shown. I guess a question on that particular test is what mediates the threshold? Is it one photoreceptor that's singing out, I saw the light? Or does some area of the visual field have to be seeing in order to pass that test?

But I think it is a useful corroboration. It made me more confident in the MLMT results, seeing that parallel. And I

don't want to leave the impression that I'm trashing your test.

(Laughter.)

DR. MASSOF: I think that it's a simple conversion to go to a scale that's more meaningful. From a clinical meaningful point of view, I think one of the definitions of a minimum clinically significant change would be one that exceeds test retest variability.

So if you're getting a change in a measure that confidently exceeds what you would expect just on a test retest, that's kind of the minimum change you would want to have in order to begin the discussion of clinical meaningfulness.

DR. BYRNE: Okay. That's helpful.

Terry?

DR. FLOTTE: So thank you. A couple of points. I mean, one point in response to (b) that I would say, and I didn't actually come out and say this in my comments before, is that I -- it certainly appeared to me that the MLMT change was clinically meaningful. So that would render (b) somewhat moot.

But on the other hand, I go back to the -- and I'll explain why. I go back to the visual function questionnaire results, which were not a primary endpoint, wasn't even emphasized as a secondary endpoint, but generated a difference that was significant at the 0.001 level.

The reason I'm going back to that questionnaire is because

in reflecting on the historical, you know, listen to the patient, the historical data from the patients' accounts are dramatic and are related to improvement in their ability to accomplish activities of daily living.

And so while I could recognize the wisdom in not trying to power a study off of a quality of life questionnaire, I think, relative to the question about using that as evidence for it being clinically meaningful, I think that adds confidence to the fact that one might be basing the efficacy judgment off of a novel assay.

DR. BYRNE: Sure. Sure. All right. Well, all that, well said. Thank you for considering Question 1.

We're going to move on to Question 2 that has two parts, and Dr. Brooks is going to lead that discussion.

DR. BROOKS: So Question 2a is at what stage of clinical presentation do the benefits of therapy outweigh the risks. I'll apologize in advance that I prepared my remarks, so I'll be covering some stuff that has already been said, of course.

So the benefit, as we've heard, of this therapy is to increase the ability to navigate and presumably to perform other activities of daily living under varying levels of low luminance.

And, of course, the benefits should be interpreted in light of the fact that the only other avenues available to these patients at present are the Argus II implant at the very

end stage of disease and supportive low vision rehabilitation.

It also, of course, presupposes that the patient has objective signs of disease and two confirmed mutations of RPE65. The Sponsor agrees with that.

The risks of treatment, by and large, are, as noted, those associated with pars plana vitrectomy, including cataract, elevated eye pressure, retinal tears and holes, inflammation, and endophthalmitis.

As the Applicant stated, two serious adverse events were noted, one in a 21-year-old individual who developed *Staph epidermidis* endophthalmitis with elevated IOP that required steroid treatment, leaving him unfortunately with irreversible optic atrophy. The second was the 19-year-old woman who developed foveal thinning, resulting in a little over a doubling of her visual angle between Days 30 and 90. I would say that this latter SAE should probably be interpreted in the light of the fact that the fovea almost certainly had significant preexisting disease and may have been more susceptible.

The other complications were either self-limiting or treatable. And Agency brought up the issue of the prednisone. And while I would defer certainly to my pediatric colleagues, it seems to me that the duration and the dose of prednisone given to these patients seems unlikely, in themselves, to lead to significant morbidity considering the seriousness of the

disease.

So when to intervene? As the Applicant points out, the prospective natural history data for RPE65 retinal degenerations are kind of hard to come by. And visual acuities, taken as one measurement, can vary significantly, even within a relatively narrow age range.

All available data, of course, point to a very early severe vision loss with a relative plateau, at least with regards to acuity, before the age of 18. Data from individuals younger than about age 4 are sparse.

It is also clear -- I don't think this point has been made -- that these patients do not spontaneously recover vision over time. And that can be the case in other inherited forms of retinal disease where gene therapy is being considered, namely Leber's hereditary optic neuropathy. Do not have that here.

Vitrectomy in young children certainly carries potential complications, as has been brought up by the discussants, introducing media opacities and refractive error, and those could be, could lead to amblyopia.

I would defer to Dr. Emerson and Dr. Lai on this point, but it seems that you would clearly -- if you were going to want to intervene before the age of 2 or 3, you would really want to be quite confident that your benefits are outweighing your risks. The Applicant's not asking for that, though.

Here, I don't think we have those data, but I think it is

a charge for us in the research community that we need to get them because I also agree with Dr. West that, moving forward, we may want to push the envelope on this.

Nonetheless, there appears to be a substantial window, at around ages 3 or 4, where the risk of introducing amblyopia would be low and the potential benefits of treatment are substantial. In fact, I had -- I perhaps erroneously thought that intervening early might decrease the risk of surgical complications, but I've been corrected in that.

And I will leave my comments at that.

DR. BYRNE: Okay. Other comments regarding this risk-benefit issue? Brendan.

DR. LEE: So I agree with much of what was just said. Certainly, from the pediatric perspective, the oral prednisone component is relatively low risk, so I don't think that's an issue at all.

But I would like to bring up another point, which is the idea of the interval, which I had alluded to earlier, between the first and second injection.

I think that if, in fact, the risk is really associated with the procedure -- and there are clearly risks with the procedure; we see a high percentage of AEs and some, you know, a few SAEs -- then I think it should be considered that even without the data that suggests, if one were to wait 30 days as opposed to 90 days, you know, the region between 18 days and

4 years, that there may be merit to that if, in fact, the data here as well as elsewhere support that there is no significant immunological problem that would, you know, be sort of contravening that approach.

I mean, the main reason for doing the sequential treatment is the potential for an immune response that would prevent a later treatment. And if that's not the case, then there may be benefits in terms of risk, of waiting.

DR. BYRNE: Okay. Yes.

DR. ZOVEIN: Ann Zovein.

So as a trained neonatal intensive care -- intensivist actually, I can speak to the infants that we take care of in our unit are much younger and more fragile and undergo much riskier procedures to preserve eyesight. So to me, you know, the prednisone and the risks associated with this is much less than, you know, what we do in neonates, to tell you the truth, to try to preserve vision.

And as regard to minimal age, I think the appropriate age to treat would just be to be able to target the largest population of terminally differentiated RPE cells that are low cycling, which was kind of some of the basis of my earlier questions. So I just wanted to share that.

DR. BYRNE: That's helpful. Thank you for that perspective.

Other comments on risk-benefit and age?

(No response.)

DR. BYRNE: Okay. We also have a Part (c) to this question, and Dr. West is going to lead that discussion.

DR. BROOKS: You skipped Part (b).

DR. BYRNE: Sorry. Keep going. Yeah.

DR. BROOKS: Okay.

DR. BYRNE: Go ahead and finish with Part (b).

DR. BROOKS: How can the -- Brian Brooks.

How can the data from subjects with advanced vision loss be extrapolated to patients with earlier stages of disease with or without measurable vision loss prior to treatment?

Here I would perhaps beg the question, because the vast majority of patients with biallelic mutations in RPE65 have some form of visual impairment from early childhood, even if acuity is not always drastically affected. From the natural history presented by the Applicant and from the published literature, it's -- as I said, it's clear that RPE65 retinal degenerations don't get better on their own.

And so I have no problem in extrapolating data from older individuals to younger individuals. And I think that, moving forward, it seems that, as Dr. West had mentioned, that pushing the envelope on the age would be contingent upon us understanding those younger patients.

DR. BYRNE: Yeah. You know, I think we did touch on that.

Any other comments on that presymptomatic treatment or

even where there's other findings other than changes in visual acuity?

(No response.)

DR. BYRNE: Okay. Now we're ready for Part (c).

DR. WEST: Part (c) was considering the adverse events associated with this subretinal injection of voretigene and the concomitant use of oral prednisone, what are your concerns for treating pediatric patients at a young age?

And I think the first part is -- the second part is easiest to deal with first, and I think that multiple panelists have addressed that oral prednisone for short-term use such as this in these doses of 1 mg/kg per day, tapering to 1/2 mg/kg per day over a period of about 2 weeks, is something that is done relatively commonly, especially in hospitals and institutions that treat children with serious illnesses.

Although it may not be done every day in a typical pediatric generalist practice, it's certainly done every day at pediatric hospitals. And so I've not been able to find any serious concerns among my colleagues at home for that.

And considering the adverse events of the subretinal injection, the concerns that I would have as a pediatric ophthalmologist would be to have a qualified pediatric retinal surgeon and pediatric anesthesiologists who would be comfortable and careful with young patients and familiar with anesthetizing, particularly, children who are sensorily

deprived and who would be anesthetized in a nurturing environment that would be safe for them and for their families.

DR. BYRNE: Okay. Any other comments about that point?

(No response.)

DR. BYRNE: I think certainly that's been discussed as part of the Sponsor's plan for making preparations at certain Centers of Excellence, so hopefully that will be carried out.

And then in Part D, Dr. Emerson is going to touch on those topics of what is the minimal age, if any, that you would recommend for treatment.

DR. EMERSON: Okay. Yeah. From the natural history data, I'm struck by the, well, the early age at which these patients meet definition of legally blind, by various definitions, by the visual acuity or also by the visual field.

And then I'm also struck by the, sort of, the spread. Even at the youngest age, some patients are doing pretty well by those measures, and some are not doing well.

So I think it is desirable to have treatment early. And then in terms of deciding what that number is for a minimum cutoff, we've heard a couple numbers already. The Phase I, the youngest patient was 8. And in the Phase III trial, the youngest patient was 4.

And Dr. Maguire talked about a 3-year-old eye being nearly full size and the RPE cells being essentially all there by 8 months. And Dr. Leroy, when he spoke earlier, was considering

even right at birth.

We do operate on patients at very young ages in retinopathy of prematurity. That's another extremely devastating, unrepairable form of blindness. Maybe Dr. Lai could comment on that, or congenital glaucoma. Those babies get very early invasive surgeries that are not less invasive than the one being proposed here.

It is my opinion that it's better to not recommend a minimum age. I think the clinician can make that decision.

DR. BYRNE: Okay. Questions? Comments?

Michael?

DR. LAI: Sure. I'll make a comment to that. And I would agree with Dr. Emerson's recommendation for the simple reason that I think there is variability in different surgeons' level of comfort and their training and their ability to operate on patients of very young age. And also, these eyes, there's enough variation that really should be considered on a case-by-case basis.

But, in general, as Dr. Maguire has pointed out, by the age of 3, anatomically, the eye is almost the same size as the adult eye. Therefore, technically, the technical aspect of the surgery would be feasible without unacceptable levels of risk.

So I think 3 is a good guideline, but there's no hard reason not to allow patients of a younger age to receive the treatment, because we currently do operate on eyes of even

younger patients.

DR. BYRNE: Yes. Go ahead.

DR. CARNEY: I would probably -- I agree and disagree. I mean, I think those younger children are much harder to operate on. The posterior hyaloid is very, very adherent, so you do have to do more manipulations and maneuvers.

You also want to have something that's a baseline for what you're trying to improve, which is the field of vision, or with this test like the MLMT. So I would say that I would actually wait a little bit longer than -- I would wait past 3; 3 to 4 maybe or even 6.

But I don't think the way that you're actually bringing back some of the changes -- or you don't know how much you're improving them right now because you have no way of measuring at that age or later. What they did with the MLMT was actually to look at a measurable object. Maybe you can teach children how to do that earlier.

But what is going to be your endpoint at 3? I mean, what are you going to be comparing it to at 10?

DR. BYRNE: Well, keep in mind that the Sponsor's proposing 3 and older and not younger subjects --

DR. CARNEY: Right.

DR. BYRNE: -- at this time. And really, part of the change of clinical practice is the clinical experience that will come from treating children 3 and older. And if it's

determined at a later date that younger ages have some advantage, then clinicians can pursue that because that'll be the treating physician's choice.

Terry, do you have a comment?

DR. FLOTTE: Yeah. Just one comment in terms of a concept here relative to age. I think Dr. High mentioned it before, but there's very good data, including human data, that suggests that vector administered to cells that are cycling, that are mitotically active, has a short duration of effect because the vector, the episomal vector genomes do not persist, while all the data that shows multi-year expression is in terminally differentiated cells.

DR. BYRNE: Right.

DR. FLOTTE: So I believe we heard from Dr. Maguire that the accepted thought process is that the target cells here stop -- don't really stop cycling till around 8 months of age. So, I mean, in whatever -- whether there's a cutoff or not, a cutoff, I think, in addition to the surgical aspects, which I know absolutely nothing about, I think the concept of doing it in the post-mitotic cells is correct.

DR. BYRNE: Well, it's probably also worth mentioning, I think, as the Sponsor has pointed out, that age is not really a proxy for severity and that one will have to make individual decisions based on your anticipated rate of disease progression and your baseline function at the time of diagnosis.

So that being said, there will be circumstances where it may be appropriate to wait because there's not significant deficits at the start. And then there may be circumstances where the findings from a mutation or the knowledge gained from the patient population would suggest a different trajectory for that patient and may want to intervene earlier.

So, Jay, did you have another comment?

DR. CHIORINI: Yeah. I just wanted to echo what Terry brought up. The other part of it is the stable cell population that the vector needs to be targeting. If the cells are cycling, the persistence of the drug will probably be a lot less.

DR. BYRNE: Yes, Ann?

DR. ZOVEIN: And then I just also wanted to speak to preservation. So by the time they're probably clinically presenting, you've lost a certain population of these cells that you can't recover. So I think there is an argument to be made to preserve cells prior to dying off due to loss of this enzyme, which may be much earlier and before people become symptomatic.

DR. BYRNE: Before symptoms present. Yeah.

Grace, you agree or want to comment to that?

Okay. Other points about age and severity in Part (c)?

Yes. Brendan.

DR. LEE: I would comment from a developmental pediatric

perspective, and I agree with many of the biological points, but from the perspective of -- and I think, relative to some of the testimony publicly, at the age of 3 to 4 is when social interaction really gets imprinted, and that's when learning occurs and playing in groups and so forth. So certainly that's an important time point to maintain visual function. So I would say that that is a key target from a developmental pediatrics perspective.

DR. BYRNE: Sure. Exactly. Okay. We're going to move on to Question 3. And Dr. Lai is going to lead that discussion. If you can -- that one -- put that one up. That's great.

So go ahead.

DR. LAI: Sure. I'll start off by reading the question.

In the clinical studies supporting the BLA, each eye received a one-time subretinal injection of voretigene neparvovec. The median MLMT score change of 2 in the treatment group of Study 301 was observed at Day 30 visit following voretigene neparvovec administration, and was maintained throughout the 1-year follow-up period. However, the duration of the AAV2-mediated transgene expression leading to sustained clinical benefits beyond 1 year is unclear.

As such, repeat administration of voretigene neparvovec may be indicated to maintain vision or delay vision loss. However, repeat administration of voretigene neparvovec in any eye was not evaluated in the clinical studies. Therefore,

there are no clinical data that address the potential benefits and risks of repeat administration of voretigene neparvovec.

And there are two parts to this question's discussion. Part (a) asks: Please discuss the potential benefits and risks of repeat administration of voretigene neparvovec into one eye.

In general, there are two broad reasons why one would want to repeat administration of any given treatment. One is there is decay in the clinical efficacy following initial administration, and the other is if there is evidence or hope that additional treatment may provide added clinical benefit.

So in the first point, you know, if this were a traditional drug, most drugs have a half-life. So after it's administered, it would slowly metabolize or clear the body. But this is not a traditional drug, and we don't have a great deal of evidence on how they will behave long term.

We know there's data in some patients going out to 9 years. And based on some of the anecdotal reports we've heard this morning, it appears that the gene expression is stable for at least that long. So there may be no need to provide an additional administration. But that would be one theoretical reason is that if, over time, it's observed that the beneficial effect of the initial administration decays.

And then the other possibility would be that, as we know, this is a progressive disease, so patients with these types of retinal diseases tend to lose vision over time. So it may be

that, over time, the natural history of the disease overwhelms the therapeutic effect from the initial administration, in which case there would be a potential reason for a repeat administration.

And, finally, we've sort of alluded to this a few times earlier with some of the questioning, which is that when this drug is administered, it treats a portion of the retina. We've heard numbers around 1/5 the retina being treated with each administration. So presumably, 4/5 of the retina is not treated. And that, potentially, is another reason to consider repeat administration.

We've seen data that patients who were treated in both eyes functionally do better than patients who were treated in one eye, presumably because more areas of the retina are rescued with two injections versus one. Might we observe the same type of added benefit if the two injections are given into the same eye instead of one into each eye?

So that's what I have prepared to start off our discussion on Part (a). I'll stop there and allow the rest of the Panel.

DR. BYRNE: Okay. Thank you. So who wants to make a comment about either the potential for a greater area of the retina as a benefit versus the risk related to immune response of repeat exposure? And maybe I'll lead off the discussion.

And, Dr. High, if you can also participate.

One of the things I think the Sponsor pointed out, there

wasn't a relationship between pre-immunity and adverse events or effectiveness. So that probably reflects the very unique characteristics of this potential space in the subretinal area and probably one of the few places in the body where this type of protection exists. So that's certainly to the advantage of the patient community where they might benefit from later administration.

And I maybe should also pay attention to the point that in the procedural protocol that you're following, there's vitreal washout to prevent exposure into the systemic compartment, where there might be an enhanced immune response to vector capsid, which would potentially block readministration or contribute to inflammation.

You want to comment about those two things while we formulate some other questions?

DR. HIGH: Yeah, thank you, because I would like to mention a couple of aspects. I mean, it is true that the eye is a relatively immunoprivileged space, and that the older concepts of anterior chamber-associated immune deviation, it now appears, also apply to subretinal administration as well and that there are a number of factors that make the eye relatively immunoprivileged, the lack of draining lymphatics, the blood-retina barrier, and so forth.

However, the Sponsor does know that based on our own dose escalation studies in animals, above a certain dose, even for

an initial de novo administration, we do begin to see focal necrosis in the retina. So there is a toxicity. There's an upper limit of drug that can be administered before one starts to see side effects. And, you know, I don't know whether those are related to an immune response or to some other toxicity, but there is an upper limit to what can be given.

And we also know, based on studies that we did during Phase III, that there is some systemic exposure to the vector. We know, based on PCR data in serum and tears, that there is biodistribution beyond simply the subretinal space at the time of surgery.

So it would seem plausible, at least to me, that your -- that the immune response to a second administration may not be exactly identical to the immune response to a first administration.

We have that slide available about Dr. Butterfield's question about the ELISpots. I will not pretend that I think that's going to illuminate the discussion, but it might be a reasonable time to show it.

DR. BYRNE: Sure. You want to go to that now? You need to switch sources here.

DR. HIGH: Okay. Here we are. Thank you.

So these show the data from the Phase III study on interferon gamma ELISpots, using as the antigen either the AAV2 capsid or RPE65 protein. So I will dispense rapidly with the

ones about the capsid because the only positives we saw -- so the cutoff -- if you see down in the bottom there, the cutoff for positivity with AAV2 was 50 spot-forming units per million cells.

There was one person who was just over the upper, upper limit of positivity at the baseline, and subsequently that individual was negative.

And there was one other person who had a higher positivity between -- we generally did these between -- less than two times, the control cutoff, 2 to 10 times, and greater than 10 times was a strong response.

So you see this individual, CH-17, at his injection baseline, 375 spot-forming units per million cells is a moderate response, but after that he was negative. So you see the, you know, this occasional positivity but then negative.

On RPE65, we saw -- what we have listed here is everybody who had any positive response. So, first, I call your attention to the fact that the cutoff for RPE65 was higher. It was 161 spot-forming units per million cells. This was derived by looking at a pool of normal donors. Okay.

So that was where we got the cutoff. You see that there was one individual, CH-22, who at their baseline was just over the cutoff for positive and subsequently negative. There was another individual who was moderately positive at baseline, 518, and after that was negative. And there was another

individual who 1 year after -- so who was consistently negatively and then 1 year later was just over the cutoff.

And then if you look in the control intervention subjects, I mean again, you see people who are either just over the cutoff or lower down, people who were a little less than, you know, still less than two times normal control.

There's one individual here, CH-36, who at baseline had positivity. This was baseline when they entered the trial, 402 spots. Year 1C was the end of their control year. Again, they still haven't seen vector. They had 1,000 spots. Thirty days after they see vector, they're up to 1,700 spots, and 90 days, 1,800 spots.

So if -- you know, we looked at these. We tried, as you see in the middle there, to correlate the positivity to what their underlying mutation was. You know, were people with stop codons or deletions more likely to have positivity to RPE65? But we couldn't find anything like that.

And so what we're left with is occasional positives. There was nothing that seemed to correlate with the clinical outcome. You know, a number of these people ended up at 1 lux, so there was no -- so, you know, to the extent that any of the immunologists in the group have insights as to what we're looking at here -- but I mean, we were very interested in this, and so we did the studies. But, you know, we saw intermittent positives without any clear correlations with clinical outcome.

DR. BYRNE: Yeah. No. Thank you for pulling this data together. I mean, clearly you're mixing two variables on top of one another, both the immune responsiveness and here's an individual who's going to hyper-responsive even without exposure and across a variety of mutations. So that's going to create, in a small study, not a clear-cut picture.

But, Brendan, do you have a comment?

DR. LEE: Yeah. I just want to comment on the molecular genetics aspect of it. You know, I think, in some genes, stop codons can often predict being CREB-negative because of nonsense media decay and mechanisms like that.

But I think, as we see more and more and, at the level of, you know, RNA and RNA-seq at many of these disorders -- not necessarily this one but other examples -- stop codons don't necessarily predict that.

So it is possible that part of the reason why you're not seeing, sort of, the correlation insight -- in fact, even though you may have someone who's -- have a stop codon in both alleles, that they are still making protein.

DR. HIGH: You mean through read-through or something like that?

DR. BYRNE: Yeah.

DR. LEE: Alternative splicing.

DR. HIGH: Yeah.

DR. BYRNE: Other comments about this point?

Yes, Lisa.

DR. BUTTERFIELD: Yeah. So thank you very much. This is very illuminating, and I certainly don't disagree with any of the interpretation, such as is able to be made at this point, and would just encourage you to collect, you know, samples for further, more detailed profiling as this goes forward, but there's clearly no pattern that arises.

DR. BYRNE: Thank you.

Other comments about this question?

Yes, Jay.

DR. CHIORINI: Yeah. So back to an earlier question that I had asked, comparing Study 101 to 102, specifically Table 15 in the BLA application, this is where you're re-dosing the same individuals from the first study, correct?

In the first study, there was no T cell response, if I understand those individuals, whereas in 102, about half the individuals, 6 out of the 11 had a T cell response. It's listed as low. My question was does that persist?

DR. HIGH: We're trying to find the --

DR. CHIORINI: Yeah. I understand.

DR. HIGH: -- table. But -- okay. Now I'm actually looking at the Table 15 in the FDA's briefing book.

DR. CHIORINI: So on page 35 in mine?

DR. HIGH: Yeah, so -- okay. Thank you. So now, just so we can put it up so everyone can see it.

Six subjects with low responses at a single time point. And just by looking at it, I cannot tell you whether that is a response to AAV2 or a response to RPE65. But for my 2 cents' worth, it doesn't matter. It does mean that, you know, as we said before, that there was some, sort of, exposure, systemic exposure to the vector, and so there was some positivity, low level, but still.

To me, what this means is that the person, at a second administration, is not the same person as at the first administration. And that, to me, is one reason that I believe very detailed studies would be required before we could be certain that readministration was safe.

DR. BYRNE: That's the perfect segue to Part (b). Thank you. What additional data, if any, would be necessary to support such repeat administration?

You want to -- panelists want to comment what would give them some comfort about that? Lisa?

DR. BUTTERFIELD: I think more detailed immune profiling. So we have a single cytokine to particular antigens, but we can now, you know, do RNA-seq and, you know, full immune profiling if you have a variety of platforms. So getting a more holistic picture of the immune responses generated, I think, would be important.

DR. BYRNE: How about strategies for mitigating other inflammation other than steroids? These are their options.

DR. BUTTERFIELD: If --

DR. BYRNE: No? Yes. Go ahead.

DR. BUTTERFIELD: If there were -- if an antigen-specific type of immune response, like to the transgene was identified, there are things under investigation now, like regulatory dendritic cell infusions, that might be able to promote tolerance, or Treg infusions.

DR. BYRNE: Okay. Brendan.

DR. LEE: Though I think, from a practical perspective, and there are certainly many biological therapies that have been tried in preclinical as well as clinical context, steroids, the oldest drug in the book, I still think is the most practical and clinically effective at some level.

DR. BYRNE: Yeah.

DR. LEE: I was going to ask, actually, a preclinical question, and for anyone, has it been modeled where a nonhuman primate been given a systemic dose of AAV2 and then an intraretinal, subretinal injection's been done to see, sort of, effects and transduction?

DR. BYRNE: You want to comment, Kathy? So the question is whether, in the face of high preexisting, preformed antibodies against AAV, there's an impact on the success of subretinal dosing, or does that change the safety profile under those circumstances?

DR. BENNETT: Yeah. Jean Bennett from University of

Pennsylvania and CHOP.

We did preclinical studies prior to the readministration to the contralateral eye, prior to the 102 study, in both affected dogs and unaffected nonhuman primates. In the nonhuman primates, we selected animals that had baseline evidence of pre-exposure to AAV2 as well as immunizing them systemically with AAV2 before it going into the eye.

We had no problem in seeing transient expression after subretinal injection in those eyes or in the dog eyes.

DR. BYRNE: Okay. That's very helpful. So that kind of confirms the possibility that there's reasonable safety even under those circumstances.

DR. LEE: Yeah. And in the context of that and what Kathy mentioned about the high-dose toxicity, then I guess you're interpreting the high dose as really an innate immune response, directly in the cell perhaps, or where it's a load of vector that's a major issue as opposed to some adaptive existing immune process.

DR. BENNETT: Yeah. One thing I want to add is we don't know if it would have been better if these animals had not been immunized beforehand. And the other thing is we did not go back to the same injected eye, which is a totally different milieu. We went to the contralateral eye, which is sequestered.

DR. BYRNE: Right. But it's also fair to say that it's

not necessarily an anti-capsid response because with an increasing dose comes an increasing level of adventitious agents that are invariably part of the vector preparation, so --

DR. HIGH: Right. So you're right. We do not know the nature of the toxicity with dose escalation, although I think we have some experiments where the transgene product was not expressed. Am I right about that? And there was toxicity that accompanied what was essentially a null vector.

So that would suggest that at least part of the toxicity is due to the capsid. But one thing that I want to add -- so Dr. Bennett is correct. We have done experiments in animals, limited, that suggest that a second administration does not carry, necessarily carry toxicity.

Over the years, I've been extremely impressed. The human cellular immune responses to AAV vectors are poorly predicted by animal studies. And I don't know whether that's because many of us carry memory T cell responses to AAV capsid or some other aspect.

But I would have only a limited degree of reassurance about the safety of this from animal studies. And it would clearly, clearly require clinical studies.

DR. BYRNE: Further word. Terry?

DR. FLOTTE: Yeah. I'd just like to make one additional point, probably more reinforcing the absolute requirement, I

think, to get a more detailed characterization of the response. And just to point out, it certainly also reinforces that the preclinical models are not predictive.

But in our experience, published both the 1-year and 5-year in intramuscular injection of AAV1, we see capsid-specific T cells with positive gamma interferon ELISpots, which on further characterization are predominantly Treg in nature.

And that particular route and serotype of administration correlates with undiminished expression over multiple years, in contrast to, I think, Dr. High's experience with systemic delivery of other AAV serotypes where liver exposure, the positive gamma interferon ELISpot correlates with an effector response that causes, in some, indication of cell injury and loss of vector expression.

So I think the point is that clearly, it's useful to do a gamma interferon ELISpot to know if there's a signal, but that would not tell you nearly enough to know if it is changing the profile for either efficacy or safety of readministration.

So I think -- you know, I think this has to be approached from the standpoint of gathering more information about the biology of the response.

DR. BYRNE: Yeah. So, you know, I think just to summarize, it's clear that there are safety -- adequate safety data at the dose levels that are recommended. This is both dose and context-specific that would influence the likelihood

of successful readministration.

Are there other comments on this point?

DR. HUNSBERGER: Yeah. I just had a question. It seems like we're talking about immunity issues, but what about surgical procedures? Is there other data that would say that okay, readministration is fine? Or is that --

DR. BYRNE: In terms of repeat access, once a vitrectomy is done, actually then the subsequent surgeries would be theoretically less complicated but --

DR. MAGUIRE: There's just no information.

DR. BYRNE: Yeah.

DR. MAGUIRE: We haven't readministered in the same eye doing this.

DR. BYRNE: So just to really recap, regarding Question 1, I think there was, around the discussion of the various ways to present the data on MLMT, in general, agreement that this was informative about the clinical meaningfulness and quality -- potentially quality of life related to patients that were involved in the study and potentially for those in future clinical use.

And then really, in summary, for Question 2 in terms of age, it at least has been recommended as it relates to the severity at baseline that the benefits outweigh the risks of the surgical intervention in the study.

So we're going to take a short break and then come on

to -- move on to Question 4, which will be a voting question. So let's -- to try to stay on time, let's be back at 3:10, give us 15 minutes break.

(Off the record at 2:55 p.m.)

(On the record at 3:10 p.m.)

DR. BYRNE: All right. We're going to turn to Question 4, if we can put that up on the screen. There we go. And this is a voting question, so we are going to ask everyone to consider this. We'll have some discussion after it's read, and then we'll vote.

But you want to go ahead and read the question?

DR. ATREYA: Considering the efficacy and safety information provided in the briefing document, as well as the presentations and discussions during the Advisory Committee meeting, do you conclude that voretigene neparvovec has an overall favorable benefit-risk profile for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy?

DR. BYRNE: Okay. So this question is now open for discussion. So let's try to get comments from everyone, if we can, before we go to the voting part. So this is really about overall favorable risk-benefit.

Comments from the Committee? We've discussed a lot of these topics related to age, related to outcomes. Any further discussion on this point?

Yes, Grace.

DR. PLUHAR: So we've heard from the testimony of the people that were involved in the study that their lives were dramatically changed by treatment. However, that was a small number of the total people that were treated. And I was just wondering whether or not everybody had -- that was treated, that had an increase in their MLMT score, had a similar change in their functional abilities that would support using this treatment.

DR. BYRNE: Correct. So in addition to the direct testimony we heard during the Open Public Hearing, can the Sponsor comment at all about, in general, the responses from patients regarding their either participation in the study or their prospect for future improvement after treatment?

DR. RUSSELL: Steve Russell, PI at the Iowa site.

We did not systematically record information. I know that for the other -- for Al Maguire and myself, the two PIs on the trial, we intentionally did not try to look at -- we intentionally avoided looking at the MLMT scores during the first year to try to avoid biasing ourselves during our examination of other components of the test.

So we were aware of who received treatment, but we did not try to correlate any of that information prior to that 1-year time point.

I don't have all of the patients, but I did go back to all

of the patients at Iowa who had a one-light level improvement, because we were interested primarily in those and what, sort of, the minimal threshold was. All of them had very heartwarming stories. I have, just as an example, two of them:

A 6-year-old who, shortly after intervention, was able to go trick-or-treating for the first time in her life with her friends. Obviously, that requires nighttime, you know, walking around.

A second, which is the second oldest patient in the trial, who was a 38-year-old who, shortly after receiving intervention, got her first job. Never had a job before and was able to maintain that. So -- also was able to go out in the evening with her friends.

DR. BYRNE: We heard something to this effect, too, in relation to some of the other comments that were made. And I think one of the unique aspects of the findings that have been presented is in many patients in the rare disease community, their principal hope is that they would arrest disease progression.

And in many circumstances we see other applications of therapeutic strategies that are intended to arrest or decline the rate of decline in a condition. And I think this is one unique finding in the study that there is actually, follows the physiology quite well in that there is actually a reversal of the deficit, which is what one would expect if there's really

the correct target engagement. And the physiologic benefit is realized in vision.

Any other comments about that?

Yes, Randy.

DR. HAWKINS: So I was concerned about safety, but I was reassured with explanations about the adverse results. So I'm reassured.

DR. BYRNE: Okay. That's important. So the terms of the risk aspects, there's a plan, and that will be implemented by the Sponsor to try to assure the most safe administration of the product when available.

DR. FLOTTE: I think one other point about the efficacy that was not, one was not able to capture quantitatively but is, I think, are things that are known to accompany visual impairment, meaning impact on learning, socialization, social learning, a variety of functions beyond the concept of just operational -- sorry -- functionality and activities of daily living. The developmental aspects seem to be substantial and not able to be fully captured in the outcome measures.

DR. BYRNE: Okay. Other comments about that? I can make one, I think, important comment about the issue that we're addressing in terms of marketing approval of a therapeutic strategy for any disease, or in particular, a rare disease: This important continuum exists between the innovation, academic health centers that are initially federally funded,

ultimately also privately funded activities that ultimately lead to availability of the product for a wider population and change clinical practice.

And that's really the goal in the end of the day is to make sure that these products are available to patients who need them. And that's, I think, what we heard during the Open Public Hearing. So this is really an important part of that value continuum of this type of personalized medicine.

Any other comments? Yes.

DR. HUNSBERGER: As a statistician, when I look at the data, I like to see if the data tells us a story. And the nice thing about this data is that it seemed like everything fell together in the same way. And so it wasn't that you had one endpoint that was significant and everything else was either marginal or not significant and then it was hard to understand. It seemed like everything made sense in the same way, and so that was very reassuring.

And I did some other statistical analyses on my own, just to see, if I did it in a different way, would everything hold up? And everything did hold up. So I think they did the right analyses, and they were very strong analyses. So I think the data was really presented in a good way, and I think everything fell together in a very nice way. So I think it's very strong data.

DR. BYRNE: Okay. I think, if there's no further comments

from the Panel, we're ready to vote. And as you can see in front of you, there's a mechanism for voting yes or no or abstentions. We hope people will choose one of those three.

And we'll all vote now. And then if there's any explanations, we'll do that following. Okay. But please vote.

(Committee vote.)

DR. BYRNE: Okay. Everyone's done. There was no music playing.

(Laughter.)

DR. BYRNE: So can we see the result?

UNIDENTIFIED SPEAKER: We're still waiting on one vote.

DR. BYRNE: I see. And when you voted, your light will remain illuminated.

Okay. Yes. Dr. Wu is not present so you can -- all right. We'll put up the vote. Now the music can play.

(Music plays.)

DR. BYRNE: Wow. So there's the result: 16 in favor, no abstentions, no votes against.

DR. ATREYA: So for the record, I need to read each one of yours voting. So okay. For the public record, Dr. Hawkins voted yes, Dr. Flotte voted yes, Dr. Emerson voted yes, Dr. Chiorini voted yes, Dr. Carney voted yes, Dr. Brooks voted yes, Dr. Butterfield voted yes, Dr. Byrne voted yes, Dr. Hunsberger voted yes, Dr. Lai voted yes, Dr. Lee voted yes, Dr. Massof voted yes, Dr. Pluhar voted yes, Dr. Raasch voted

yes, Dr. West voted yes, Dr. Wu is not available, Dr. Zovein yes -- voted yes. So it's a 16 out of 16 unanimous vote.

Thank you.

DR. BYRNE: Okay. Thank you all. This now concludes the meeting, I believe. We're done. Thank you very much for your service, and thank you to the Sponsor for their presentations.

(Whereupon, at 3:20 p.m., the meeting was concluded.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

67TH MEETING OF THE CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE

October 12, 2017

Silver Spring, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Biologics Evaluation and Research.

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Tom Bowman

Court Reporter