FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE DERMATOLOGIC AND OPHTHALMIC DRUGS ADVISORY COMMITTEE (DODAC) AND THE OPHTHALMIC DEVICES PANEL OF THE MEDICAL DEVICES ADVISORY COMMITTEE (OP-MDAC)

Tuesday, February 24, 2015

8:04 a.m. to 5:24 p.m.

FDA White Oak Campus

Building 31, The Great Room

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:04 a.m.)

Call to Order

Introduction of Committee

DR. AWDEH: Good morning. I'd like to first remind everyone to please silence your cell phones, smartphones, or any other devices, if you have not done so already. I would also like to identify the FDA press contacts, Stephen King and Timothy Irvin. If you're present, please stand.

With that, I'd like to start the joint meeting of the Dermatologic and Ophthalmic Drug Advisory Committee and Ophthalmic Device Panel of the Medical Device Advisory Committee of the FDA.

My name is Richard Awdeh. I'm a corneal refractive surgeon and assistant professor of ophthalmology, pathology, molecular biology and biochemistry at the Bascom Palmer Eye Institute in Miami, Florida.

I'd like to go around the table and ask each member or consultant, FDA panel and DFO to introduce themselves with their name and

affiliation. Why don't we start on this side over here?

DR. EYDELMAN: Good morning. Welcome. My name is Malvina Eydelman. I'm director of the Division of Ophthalmic and ENT Devices in the Center for Devices and Radiological Health, or CDRH.

DR. CHAMBERS: Good morning. I'm Wiley Chambers. I'm the deputy director for the Division of Transplant and Ophthalmology Products in the Center for Drug Evaluation and Research.

DR. BOYD: Good morning. My name is William Boyd. I'm the clinical team leader in the Division of Transplant and Ophthalmology Products in the Center for Drug Evaluation and Research.

DR. ZHUANG: Good morning. My name is Dongliang Zhuang. I'm a statistical reviewer at the Division of Biometrics IV, Center for Drug Evaluation and Research.

DR. OWSLEY: Good morning. I'm Cynthia Owsley. I'm a professor of ophthalmology at the University of Alabama at Birmingham. Sorry, my

voice is going. And my research area is aging-related vision impairment and eye disease and patient-reported outcomes.

DR. HUANG: Good morning. I'm Andrew Huang. I'm from Washington University in St. Louis. I'm a professor of ophthalmology. I'm a corneal specialist.

DR. MacRAE: Good morning. Dr. Scott MacRae, University of Rochester, professor of ophthalmology, professor of visual science, and corneal specialist and work in optics, as well.

DR. JENG: Good morning. I'm Bennie Jeng from the University of Maryland, professor, corneal and external disease specialist.

DR. OLIVIER: Good morning. Mildred Olivier, professor of surgery, Division of Ophthalmology at Chicago Medical School and founder of the Midwest Glaucoma Center, glaucoma specialist.

DR. YOO: Good morning. David Yoo, associate professor of ophthalmology at Loyola University in Maywood, Illinois and ophthalmic

plastic and reconstructive surgery and residency director.

DR. WEISS: Jayne Weiss, chair and professor of ophthalmology, pathology and pharmacology at LSU in New Orleans and corneal refractive surgeon.

DR. CHOI: Moon Hee Choi, designated federal officer.

DR. FEMAN: Good morning. I'm Steve Feman. I'm an ophthalmologist. I'm professor of ophthalmology at St. Louis University, and my research is in public health and ophthalmology.

DR. McLEOD: Stephen McLeod, University of California-San Francisco, corneal external disease refractive surgery.

DR. BROWN: Jeremiah Brown, retina specialist in San Antonio, Texas at the Brown Retina Institute and clinical associate professor at the University of Texas Health Science Center in San Antonio.

DR. EVANS: Good morning. Scott Evans, biostatistics at Harvard University.

DR. BELIN: Good morning. Michael Belin,

professor of ophthalmology and professor of vision science, University of Arizona, corneal refractive surgery.

DR. SUGAR: I'm Joel Sugar, University of Illinois at Chicago. I'm a corneal specialist.

MR. MATSON: Good morning. I'm Tracy Matson, patient representative from Little Rock, Arkansas.

DR. LEGUIRE: Larry Leguire, consumer representative.

DR. CORCORAN: Good morning. Gavin Corcoran. I'm the chief medical officer at Actavis, and I'm the industry representative for DODAC.

MR. PFLEGER: Good morning. Michael Pfleger. I'm with Alcon, a division of Novartis, and I'm an industry representative.

DR. AWDEH: Thank you.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and

open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairman. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during the breaks or lunch. Thank you.

Now, I'll pass it on to Moon Hee Choi, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's meeting of the Joint Dermatologic and Ophthalmic Drugs Advisory Committee and the Ophthalmic Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

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

compliance with federal ethics and conflict of interest laws.

Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves New Drug Application 203324 for riboflavin ophthalmic solutions with

UV-A irradiation submitted by Avedro, Incorporated. The combination products are used in corneal cross-linking and proposed to be indicated for the treatment of progressive keratoconus or corneal ectasia following refractive surgery.

This is a particular matters meeting during which specific matters related to Avedro's NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

In accordance with the charter of the Medical Devices Advisory Committee, the consumer representative for the Ophthalmic Devices Panel, Dr. Larry Leguire, is non-voting.

With respect to FDA's invited industry

representatives, we would like to disclose that Michael Pfleger and Gavin R. Corcoran are participating in this meeting as non-voting industry representatives acting on behalf of regulated industry. Mr. Pfleger's and Dr. Corcoran's roles at this meeting are to represent industry in general and not any particular company. Mr. Pfleger is employed by Alcon and Dr. Corcoran is employed by Activas.

We would like to remind members and temporary voting members that if the discussions involving any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue.

Thank you.

DR. AWDEH: Thank you. We will now proceed

with Dr. Chambers' introductory remarks.

FDA Introductory Remarks - Wiley Chambers

DR. CHAMBERS: Thank you very much. I would like to add my personal welcome to all the advisory committee members and guests. I recognize this time of year, sometimes travels are a challenge.

The product we will be discussing today is a combination product. The Office of Combination Products has determined that the primary mode of action for this product is the drug action and, therefore, the Center for Drug Evaluation and Research is the lead center.

This is a combination product which was submitted as a new drug application under 21 CFR Part 3, which is the combination products. The study protocols were conducted under an IND. There was an NDA submission. The advisory committee that we have convened today is a combination of both the Drugs and Devices Panel combined as one committee.

The Center for Device Evaluation and Radiologic Health consulted on the NDA.

Today you will hear a presentation by

Avedro, the applicant for this application. Then there will be a presentation by the FDA. We will allow time after lunch for an open public hearing, and then we will go through a number of discussion topics and questions, and finally end with two voting questions.

If there are any questions at any point, please feel free to ask them, express your opinions. The agency has not come to a decision on this application. People will express various points of view, various bits of information to you. We are interested in your feedback and comments to us.

Again, no final decision has been made on this application. There is a large review team for various members, only some of which you'll hear. There are other pieces that are also under review, but will not get presented because we don't feel there's necessarily the expertise on this group; chemistry, manufacturing, some different aspects that we don't typically present to an advisory committee. But we are very much interested in your

opinions on this application.

Thank you again for your time.

DR. AWDEH: 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 advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have such financial relationships. If you choose not to address the issue of financial relationships at the beginning

of your presentation, it will not preclude you from speaking.

We will now proceed with the sponsor's presentations.

Sponsor Presentation – David Muller

DR. MULLER: My name is David Muller. I'm the founder and CEO of Avedro. First of all, I'd like to thank FDA for convening this meeting and allowing us the opportunity to present our information to you, and also thank all the panel members for taking the time out of what I'm sure is a very busy schedule to come and hear what we have to say.

So just a brief company overview. I founded Avedro in 2007 as a medical device and pharmaceutical company. Currently, we have approximately 100 employees based in Waltham, Mass. And our mission, which I believe we're accomplishing, is to advance the science of corneal collagen cross-linking with the goal of helping patients with corneal disorders.

We have developed a team of scientists who

have elucidated most of the mechanisms behind cross-linking, and I think our team is well positioned to move corneal cross-linking forward in the world.

Product overview or the process overview, collagen cross-linking was first developed by European researchers in Dresden in the late '90s. The concept was that by using a combination of riboflavin and UV to generate reactive oxygen species, the net result will be a strengthened cornea.

The first patients were treated in early 2003. And the goal, again, was to strengthen the cornea, initially looking at keratoconic patients and then moving on to looking at post-LASIK corneal ectasia patients.

So far around the world, certainly several hundred thousand patients have been treated with this modality, with our device alone, our device and a drug product. Over 75,000 patients have been treated for the two indications that we're seeking approval for.

The clinical study history has a little different path than most. It was originally started in 2007 by a sponsor that ultimately could not afford to bring the trials forward. They were started also at a time when there was very little clinical knowledge about what the progression of cross-linking was with respect to healing.

In 2010, we acquired the rights and the ownership of the three studies that were underway, UVX-001, 002 and 003. At the time we took over the trials, all the patients in the trials had been treated, and there were no more treatments done of the primary study after we took over the trial.

We finalized our statistical plan the end of December 2011-January 2012. There had been a prior publication from one of the single centers on data from the study, and the prior sponsor had done an interim analysis on the data.

Initially, when the initial sponsor sought to start the IND, they had asked for a 3-month time point. And at that time, there was very little literature for them to understand what was going

on. A 3-month time point just turns to be the wrong place to look because of the corneal healing that takes place. In fact, the FDA had originally recommended to the sponsor that he choose a 12-month time point.

As I said, when we took over the trial, all the patients were treated. We really, at that point, had no choice but to extend the primary endpoint to 12 months because, as you will see in the data, at 3 months, the patients are still too early in the healing process.

Also, at that time, there was much more literature. There was probably about five times as much literature that had been published on these patients, and so we had a much better understanding of where the endpoint should be. But I would like to emphasize that, again, all patients were treated, and our analysis was not impacted. We were not able to impact the study by our change of the endpoint.

So our proposed indication is for the treatment of progressive keratoconus and corneal

ectasia using UV light and riboflavin solutions. I think it's important to point out these are orphan drug indications. As most of you know, it's certainly an unmet need that exists today for this orphan disease.

The presentation agenda, first, Dr. Raj Rajpal is going to get up and give you an overview of the disease, the background of the disease, the mechanism of action, and where the real unmet need is.

I will come back up and give a presentation about the device and drug description itself that we're seeking approval for. This will be followed by Dr. Peter Hersh, who will go into detail on the phase 3 studies, and then I will appear one more time for a brief summary.

In addition to the people I just mentioned for potential responders, we have with us Pam Nelson, who is VP of Regulatory Affairs; Vineeta Belanger, VP of Clinical Affairs; Evan Sherr, vice president of Advanced Product Development; Dr. Robert Gibbons, professor, University of

Chicago, statistical consultant; Maureen O'Connell, regulatory device consultant; and, Chris Peterson, an engineer consultant to help us out on that end.

So with that, I will turn it over to Dr. Rajpal.

Sponsor Presentation - Rajesh Rajpal

DR. RAJPAL: Good morning. I'm Raj Rajpal. I'm a corneal specialist, and I practice here in the Washington, DC area. I also would like to add my thanks to the members of the advisory committee, as well as the device panel and representatives of the FDA, to share some thoughts today on keratoconus and corneal ectasia.

I'm a clinical investigator with Avedro and on the medical advisory board, and as such, in terms of financial disclosure, I do have a small equity interest, as well as receive funds for research and associated expenses.

I know that most of you, as clinicians, already understand the cornea, the disease, and the mechanism of action. But I'm going to try to set a framework for our discussion by going over the

basics of a lot of this first. And then I'm going to try to discuss a little bit about where there's an unmet patient need in the U.S.

So I think perhaps to start with, one can think of the cornea as a very special lens on the surface of the eye, special because it provides approximately two-thirds of the refracting or focusing power of the eye.

The normal cornea has a micro-architecture that allows it to maintain a rigid shape and a smooth curvature. The fibrils of the collagen within the cornea are structured in an orderly fashion to transmit light with minimal distortion.

In disease conditions, however, the cornea can develop a significant amount of irregularity. One can think of keratoconus as occurring naturally and of corneal ectasia as a condition that occurs in patients who have undergone prior refractive surgery.

Basically, the cornea is structurally weak in these two conditions, and progressive deformation leads to architectural and optical

distortion. You'll see throughout the presentation today topographic images. Generally think of red as representations of high points or steep parts of the cornea.

Visually, we think of aberrations within the eye's optical system, and an irregular cornea will cause this and ultimately diminish visual function. On the slide on your left, you can see, from the side, a very distorted cornea with what we consider a very significant cone inferiorly.

Symptoms that patients complain of are typically ghosting, glare, halos, starbursts around light, multiple images, and you can see depictions of some of these on the slide right now.

So as corneal specialists, we all see patients daily in whom these conditions have a significant impact. Keratoconus is generally thought of as a disease of the young. In many studies, it has had an average age of onset on the teenage years. And as you can imagine, since this condition progresses, over the next several decades, this can have a significant impact on

patients' lives. This is the time when they're going through their educational process, making career choices, and, ultimately, if they can't function well visually, they have limited options.

Corneal ectasia, relatively speaking, affects a slightly older population because these patients have already undergone a surgical procedure, typically LASIK. Both conditions are progressive diseases that can cause an increase in corneal distortion and in severe cases, scarring, that ultimately leads to a loss of visual function and frequently the need for corneal transplantation.

So how do we manage these patients currently? Well, rigid or specialty contact lenses are really the mainstay of treatment. You can think of this as a new lens that's basically masking the irregularity of the cornea beneath it.

These lenses, however, are often difficult to fit, require frequent office visits by the patients to their provider, and, most importantly, contact lenses do not limit the progression of the

disease. However, as the disease progresses, patients have a harder and harder time tolerating the use of contact lenses.

Surgically, we have the option of intracorneal ring segments. These are done to try to improve the symmetry of the cornea. These certainly are not applicable to all patients and still frequently require the use of contact lenses after placement, and, ultimately, again, do not limit or cause the disease progression to stop.

So ultimately, patients that are contact lens intolerant or are not able to function well visually because of scarring or other reasons end up with the option of a corneal transplant, and certainly as corneal specialists, we try to delay and hopefully prevent a corneal transplant as long as possible.

It's estimated that approximately 30 percent of all penetrating keratoplasties, full thickness transplants, in the U.S. -- so approximately 6,000 patients per year -- are due to keratoconus.

Corneal transplant patients have a long

visual rehabilitation process, frequent office visits, removal of sutures, control of postoperative astigmatism, frequently with contact lenses, occasionally with other secondary procedures, and certainly we monitor these patients for the risk of infection and the ongoing need for monitoring for rejection and the use of steroid medications frequently.

Over a 20-year period, it's estimated that approximately 70 percent of corneal transplants will fail. So especially in that younger patient age group that is affected most by keratoconus, this can mean the need for multiple corneal transplants over a lifetime.

So let's talk about the rationale for cross-linking. So as we've discussed, keratoconus and corneal ectasia are inherently biomechanical problems that have caused a weakened cornea. The goal of collagen cross-linking is to strengthen the cornea by increasing the corneal rigidity, ultimately stopping the progression of disease and improving the prognosis of disease so our patients

can function better.

How does it work? Riboflavin, vitamin B2, acting as a photosensitizer, combining with UV light at a wavelength of 365 nanometers on the surface of the cornea creates an activated form of riboflavin and reactive oxygen species. These interact with collagen and glycosaminoglycans in the corneal stroma to form cross-links.

So in essence, cross-linking improves the biomechanical properties of the anterior portion of the cornea by strengthening the tissue. And as you can see on this slide, an example of a control section of cornea that is relatively flexible, where as a portion of cornea that is cross-linked has significant rigidity.

It's estimated that Young's modulus, which is a measure of elasticity, can be increased greater than fourfold by the effect of cross-linking on the cornea.

We've come to learn that after the relatively quick cross-linking process, there's significant remodeling that still has to occur.

Initially, the epithelium has to heal back, typically in about five days, and then there is significant epithelial and stromal remodeling that can take several months to occur.

We've also come to learn that this remodeling effect seems to be persistent. In a recent study that was published by Wittig-Silva, three-year results of patients using the Dresden protocol, same as in the clinical trials that you'll be hearing about shortly, where the control group, untreated, continued to deteriorate with their keratometric measurements being 1.75 diopters greater, whereas the study group at three years had one diopter of flattening.

In another series, 10-year results, patients followed for an extended period of time with the same protocol, and mean K flattened by approximately 5 diopters. Steep K was approximately 3 diopters of flattening, and best spectacle corrected vision improved by approximately 1.5 Snellen lines over that 10-year period.

So our patients have a challenge. There is no FDA-approved drug therapy for these orphan populations that actually treats the disease. Many of our patients and their family members are anxious, desperate to seek treatment, frequently look at options to go overseas for this. They frequently look at procedures or options for procedures performed in the U.S. with products that are not approved for cross-linking.

These are devices that often have been brought over from international sources or drugs that are being made in compounding pharmacies that may not have very standardized oversight. So ultimately, I think clinicians and our patients need appropriate labeling to be able to address their options for treatment better.

Finally, let's talk about the unmet patient need in the U.S. I think we understand that cross-linking is the only treatment that we have available that truly treats the pathophysiology of the compromised biomechanical integrity in the cornea.

Again, as corneal specialists, we all understand the reasons that we want to limit or delay the need for corneal transplantation, the associated issues that we discussed with visual rehabilitation, the time that it takes before patients can wear contact lenses again, before they can function as normally as they would like to in terms of physical activities. And ultimately, our goal is to retain enough visual functioning for our patients to be able to use their glasses or, most commonly, their contact lenses to function normally and avoid the need for surgical intervention.

So if I could share a quick anecdote about a patient, a young man whose vision had progressed significantly over two years, and his parents had noticed that this coincided with a significant decline in his ability to function at school, in academic activities, and athletic activities. He was diagnosed with keratoconus. They looked into all the treatment options. It was progressing rapidly, and ultimately we're considering a corneal transplant.

Fortunately, he was able to meet one of the studies' inclusion criteria, not in this area, but had to be sent elsewhere, because at that time we didn't have a study that was able to include him, and he ultimately had cross-linking.

Over the 6 to 12 months afterwards, his parents described to me a significant change. He was able to function better in school, much better in social interactions, and, most importantly to him, what he wasn't able to do prior to surgery, he was able to take the driver's test, meet the visual criteria, and pass and get his driver's license. And that was one of the most important things in his life at that time.

But ultimately, just as an example, this is someone who otherwise would have likely needed a corneal transplant, and to date now, as he's getting ready for college, he has been stable and has not progressed. And so this has had a major impact on his life.

So I would ask, in closing, that as you listen to the data and the comments today, you keep

in perspective that these patients truly have limited options right now, and they truly will benefit from having in the U.S. a treatment option that can prevent their condition from worsening, hopefully improve it, and limit their need for other surgical intervention.

So again, I thank you for your time, and I will ask David to come back up.

DR. MULLER: Thanks, Raj.

This will be fairly brief, but I'd like to just discuss what it is we're actually looking to get approved.

First of all, the riboflavin ophthalmic solutions. As you've just heard Raj speak about compounding pharmacies and the like, I think there's often a tendency to think of riboflavin as something we're buying at Walgreens and could be used in the patients. Far from the truth.

Working with the FDA, we've developed a full riboflavin 5'-phosphate, which is manufactured under full cGMP conditions in an FDA-registered and inspected facility. In fact, our riboflavin

5'-phosphate is, I believe, the only such product made anywhere in the world.

The drug product itself is made, again, in a cGMP FDA-registered and inspected facility. There are two products. There is Photrexa, which is the riboflavin basically in saline, and Photrexa Viscous, which has dextran in it for thickening the riboflavin and being able to hold it in place on the cornea during the course of the procedure.

The device that we're seeking approval for is the KXL system. The UVX system is what was used in the clinical trial that the original sponsor had. We developed the KXL system, again, manufactured under QSRs in an FDA-registered and inspected facility. We've done significant testing to demonstrate the equivalence of our device in the clinical system, and I'm going to show you a little bit of that now.

Our plan to submit the NDA with the KXL system was discussed with FDA in a pre-NDA meeting. We discussed the comparability plan of what was needed to show the comparability. FDA asked a few

questions. We responded to all of those, and I'm going to show you a couple of those now in the next couple of slides.

So on the device side, I would say focus on the bottom right-hand corner, what's written there and it's the most important thing. Both devices are LED-based devices. Both deliver light at 365 nanometers, with an illumination intensity of three milliwatts.

So remembering we're drug-device combination, the device provides a dose, too, and this is the metered dose.

The UVX system, which was originally in the trials can be seen on the right, it was an early design. You see the pole there, and that pole was designed to hold the system on a C-clamp next to the patient and provide for the physician to try to align the device. I'll show you a little more detail of that in a moment.

Our device, on the left, you can see, besides looking significantly different, the features that it adds is the articulating arm,

which allows much more precise positioning over the patient, along with actually a joystick control for micro-positioning with the patient, so adding to both patient comfort and to physician usability.

So again, what's the important feature? The important feature is that we're at the correct wavelength. This is a spectrum that shows the overlapping spectrums of the UVX system and the KXL system centered at 365 nanometers. So these, in fact, I believe, use the same company's LEDs. So the light is the same from the devices.

How about the light delivered during the course of the procedure? Spectral output for the device is identical. The UV irradiance, again, three milliwatts for both systems, identical. UV exposure time, 30 minutes to get the appropriate dose from what is known as the Dresden protocol, 5.4 joules per square centimeter.

So this is the dosing and this is what the KXL system and the UVX system both provide.

As I mentioned, there was the issue with respect to alignment ease. So the patient on your

left is a patient being treated with the UVX device. The alignment was done principally by looking to move the device down near the eye to get the appropriate focus, and then the physician was actually required to use a ruler to measure the distance between the bottom of the lens and the eye, a very difficult addition to the procedure.

On the left, again, you see the telltale UV fluorescence for the riboflavin, but also you see the crossed red lines on there. Those are lines that provide both X, Y and Z control of the beam, and the physician controls that with a thumb-wheel joystick. So that during the course of the procedure, which is a half an hour, should the patient move or drift, the physician can easily keep the beam centered on the eye. But again, it's still three milliwatts and delivery 5.4 joules.

One of the other features that we changed was we changed what's called the working distance. This is the distance between the bottom of the device and the patient. This was done from a working distance perspective to give the physician

more room under the device to be able to continue to wet the cornea or provide riboflavin and also provide for patient comfort because it moves the device away from the patient and makes them less claustrophobic.

But for those of you who know very simple ray tracing, you can see that the net effect is that at the eye, there is the same amount of irradiance, same beam diameter, same fluence and all. So by changing this around, we've actually made the system better, but have not at all changed the safety and efficacy.

In the original sponsor's protocol, he chose to have three spot sizes, 7-and-a-half, 9-and-a-half, and 11-and-a-half. During the course of the trials, no patient were treated at the 7-and-a-half. Ninety-one percent of the patients that were treated at 9-and-a-half, and there were several patients that were treated at 11-and-a-half. But the bulk were at 9-and-a-half.

So we chose as our spot size a nominal 9 millimeters, and that's 9 millimeters plus or

minus about a half. And what you see is the typical topography of a keratoconic patient, full 9 millimeters. And the little dotted lines around the outside are the dotted lines with respect to 9-and-a-half millimeters for the original sponsor's size and our 9 millimeters. In fact, they really basically overlap in that range. So the full cornea is treated during the course of the procedure.

So I think from the device side, I think we've shown 100 percent equivalence; and, from the drug side, on the riboflavin, we are actually the only company in the world that has the ability to offer really truly regulated riboflavin solutions.

So with that, I'll turn it over to Dr. Hersh, who will describe the clinical studies.

Sponsor Presentation - Peter Hersh

DR. HERSH: Thank you and good morning. Peter Hersh. I'm a corneal specialist and clinical professor of ophthalmology at Rutgers New Jersey Medical School. First, I would like to thank the panel for being here today, FDA and public

representatives.

I serve as medical monitor for Avedro, and in this capacity, I am a paid consultant and have a small equity interest in the company. But my interest in keratoconus goes back actually several decades.

Myself and my practice have always been interested in KC from both the research and clinical points of view. And, indeed, my first project in third grade was drawing out keratoconic contact lenses for my father, who was an optometrist, who had an interest in keratoconus back in the '60s and the '70s.

So my interest in this subject goes back a long ways, and when Avedro started to participate in cross-linking studies, I was very happy to work with them on it.

The rationale of cross-linking and the purpose of doing cross-linking in our patients is to strengthen the cornea in keratoconus and ectasia, which are inherently biomechanical diseases of the cornea, with increased progression,

increased corneal distortion, and increased the spectacle in contact lens intolerance.

So the clinical benefit is to slow the natural progressive time course of these ectatic corneal disorders. We want to keep that topography as stable as possible.

To do this, we conducted three prospective, randomized, open-label, controlled, parallel group clinical trials over a 12-month period. In these studies, patients were randomized to one of two groups, a cross-linking treatment group and a control group. The planned study size was 160 eyes, subsuming 80 eyes in the control group and 80 eyes in the treatment group.

As mentioned before, 3 months after the procedure, after the 3-month follow-up, the patient could have both the nonrandomized fellow eye treated, so the patient's other eye could be treated, and, similarly, the control eye at that point could cross over and have the cross-linking treatment.

These are the clinical study sites. They

comprise both academic centers, as well as private practice cornea subspecialty practices.

The cross-linking procedure that was done was consistent amongst the three study trials. We used the standard Dresden protocol, the first step of which is epithelial removal over the central 9 millimeters of the cornea. At that point, riboflavin drops were administered every 2 minutes for 30 minutes.

To assure complete uptake of riboflavin into the corneal stroma, patients were taken to the slit lamp and observed. We inspected for complete corneal saturation and also looked for anterior chamber flare as evidence of complete penetration and saturation of the riboflavin solution.

At that point, the corneal thickness would be checked. If greater than 400 microns by ultrasonic pachymetry, we would proceed with ultraviolet treatment. If less than 400 microns by ultrasonic pachymetry, the patient would have riboflavin without dextran, that is, hypotonic riboflavin drops administered every 10 seconds for

two-minute sessions. At the end of each two-minute session, we would again check the thickness of the cornea. Once the cornea reached 400 microns, the patient then proceeded with UV treatment.

Ultraviolet exposure was 30 minutes at 365 nanometers, 3 milliwatts per centimeter square, for a total dose of 5.4 joules per centimeter square. During the time of ultraviolet administration, there was continued administration of riboflavin drops every two minutes.

The cross-linking group is, as we just discussed, on the left side. If you look at the right side, the control group specifically had no epithelial removal. They did have administration of the same riboflavin drops every 2 minutes for 30 minutes. They then went under the ultraviolet lamp, but the lamp wasn't turned on. So they gazed at an un-illuminated ultraviolet light with continued administration of the riboflavin every 2 minutes.

Inclusion criteria. Patients needed to be 14 years of age or older, with a diagnosis of

either progressive keratoconus or corneal ectasia. Axial topography needed to be consistent with KC or ectasia. And in addition to this, the steep K reading needed to be 47 diopters or more, and the inferior/superior ratio, that is, the degree of asymmetry on the corneal map, needed to be 1.5 diopters or more. All of these topography maps were vetted at an outside study center. Best corrected vision needed to be worse than 20/20 on the ETDRS chart and total corneal thickness greater than or equal to 300 microns.

Now, importantly, as we continue to discuss the analysis, KC patients needed to demonstrate progression over the previous two years. This could be historic or it could be by individual site measurements and include an increase of a diopter or more in the steepest K value, be it manual or simulated; an increase of a diopter or more in manifest refraction; and, other indicators of corneal progression, as you see here.

Exclusion criteria included history of corneal surgery or intra-corneal ring segments and

any history of a corneal disease that would interfere with healing after the procedure, chemical injuries or herpetic eye disease and the like.

The primary efficacy measure for the study was a quantification of corneal curvature by corneal topography, which was the maximum keratometry. So Kmax, maximum keratometry, was chosen as our primary efficacy measurement. Kmax is derived from computerized corneal topography analysis. It is read by the software in the equipment, and it is a feature of topography that I think measures the salient aspect of ectatic corneal diseases; that is, how high is the cornea, how steep is the cornea, and, in essence, how irregular is that cornea? What is the quantity of the bulge in these ectatic corneal problems?

It's an objective endpoint, it's a quantitative endpoint, and, importantly, it was consistent among study sites. All study sites used the same equipment, in particular, the Pentacam High Resolution Scheimpflug imaging device and the

same software, as well, that defined maximum keratometry on the corneal map.

Now, the endpoint of the study was evaluated over time by change in Kmax. Study success was defined as a difference of 1 diopter when we compared the progression of the keratoconus group to the progression of the control group; that is, we looked at Kmax at baseline, Kmax at one year to define progression of the corneal disease, and did this for both treatment and control groups. A difference in 1 diopter was our primary efficacy endpoint.

Now, as I mentioned before, there was an extension in timing of the efficacy analysis from 3 to 12 months based on our clear understanding over the years of the timeframe of epithelial healing and corneal remodeling after the procedure. And 3 months simply is too early a time in these progressive disorders. And in a procedure in which there's corneal epithelial healing, 3 months is too early a time point to properly assess efficacy.

However, the criteria for study success was

unchanged. Again, no change in the endpoint of 1 diopter or difference between treatment and control.

So let's look at the results of the study. There were three clinical trials, UVX-001, 002, 003. For ease of presentation, I'm going to concentrate on the results of pooled analysis, consisting of 001 and 002 or 001 and 003 in the ectasia analysis.

First, we'll look at progressive keratoconus. 205 eyes were randomized in the KC study, 102 to the cross-linking group and 103 to the control group. About 86 percent of patients completed the entirety of the study through 12 months. A substantial number of those patients who were discontinued from the study were discontinued because there was one study site at Emory, where the investigator left the institution, and the study was closed.

Looking at some baseline demographics, average age of patients was 33 years old. Average Kmax was similar in the early 60s between the

treatments and the control group. There was about a 2 to 1 preponderance of males over females in the clinical trial.

Now, again, I had mentioned that patients were allowed to cross over at the 3-month follow-up visit, and this slide shows the timing of those crossovers. Simply turning your attention to the bottom row, there were 103 control eyes initially enrolled. At 3 months, 101 remained in the study.

At 6 months, between 3 and 6 months after the 3-month evaluation was done, 57 of these control eyes crossed over and had treatment, leaving 39 observable eyes. And at one year, 33 additional patients had crossed over between 6 months and a year, leaving two control eyes at the one-year time point.

Now, this, of course, led to some difficulties in ultimate study analysis and statistical analysis. And because of this, we used a last observation carried forward method. This is a method that's used to impute missing data for the 12-month analysis. That is, for control subjects

that crossed over to treatments, the efficacy data, that is, that is their last observed efficacy data, be it at 3 months or 6 months, was carried forward to the analysis at 12 months.

The LOCF in this population seems quite valid for imputation because, remember, these are progressive conditions. They're conditions where there is no spontaneous remission or improvement. When we use the last observation carried forward, we are presuming that there's no further progression in those patients when, in fact, one might expect, since these patients were previously progressive, had shown progression early on, that they would continue to progress. So LOCF as a methodology is a rather conservative methodology to look at our endpoint.

So let's look at the results. This slide really is the salient results slide of the clinical trial. The treated keratoconus group, over the course of a year, improved. So this is a progressive population that had been getting worse over the preceding two years, and you can see here

that there was 1.6 diopters of flattening in the treated group.

This is compared to the control group where you see continued worsening, continued progression and steepening of the condition. And recollect, again, this is the last observation carried forward. So one might expect that if all patients were indeed available at 12 months, that there would have been even continued and more progression than we see in the control group here.

So the difference between treatment and control over the course of a year is 2.6 diopters. Our endpoint was a difference of 1 diopter or more. So we can see that the endpoint was met and met quite convincingly. This met our definition of success and was statistically significant.

When doing this analysis, there were other sensitivity analyses used aside LOCF, and these corroborated statistically the results.

As you know, there's a wound healing time course after a cross-linking. And if we simply look at those eyes that were treated in the

randomized eye group, you can see that there's indeed improvement over time.

These progressive conditions improved by half diopter on average in 3 months, by a diopter at 6 months, and by 1.6 diopters at 12 months. So at both 6 months and 12 months, looking at the treatment group alone, the primary efficacy criteria of one diopter was satisfied, even disregarding the control group. So these patients indeed are getting better.

Compared to the control group, we see a similar time course with improvement in outcome and improvement in the difference between treatment and control over the course of 12 months, meeting the endpoint criteria of a diopter at 3 months, 6 months and 12 months, 1.1 diopter difference, 2 diopter difference, and, finally, 2.6 diopters difference at the 12-month time period.

Here we present the data looking only at observed eyes. So this did not use LOCF imputation of data. So these are all observed eyes in the randomized treatment and randomized control group

at 3, 6, and 12 months, and this is very similar to the slide that we saw before.

There is improvement over time. There is continued differentiation of the treatment group and the control group over time, meeting our endpoint criteria at both 3, 6, as well as 12 months, and, similarly, a difference of 2.6 diopters at the 12-month study point; again, compared to an endpoint criteria of 1 diopter or more of difference.

To further look into the data, we took all treated eyes. So these are the initial randomized eye, the fellow eye that was treated, and those control eyes that crossed over. Here you can see we have well over 200 study eyes.

Recollect, again, these are patients who had been worsening before the baseline. You can see here a typical time course of cross-linking, where there's a little worsening secondary likely to epithelialization, epithelial healing in a month, and continued improvement thereafter.

When we look at the all-eye analysis, this

corroborates our other analyses with 1.6 diopters of improvement in the treatment group alone. So these are the KC eyes, looking at all of them, an average of 1.6 diopters of topographic improvement, again meeting our endpoint criteria.

Now, when counseling patients who are going to undergo a procedure such as cross-linking, though mean change is helpful, it is also interesting to look at stratified changes amongst individuals.

So in these 89 observed eyes, the average change, again, in these keratoconus patients was 1.8 diopters. But importantly, as we look at this bar graph, 73 percent of patients improved, that is, flattened their baseline Kmax over the course of a year. So about three-fourths of the patients improved their corneal topography.

Indeed, if we look at the bar way to the left, approximately 32 percent of patients improved their corneal topography by 2 diopters or more, really a clinically substantial improvement.

If we go to the other side, there were

5 patients who continued to progress in their corneal topography by 2 diopters or more. Of course, remember, these conditions were progressive initially. So we don't know if those patients who continued to progress are progressing at the same rate or maybe progressing at a slower rate because of the cross-linking procedure.

Looking at the pediatric stratification, eyes were treated in patients 14 years of age or older; 7 eyes were in patients less than 16 years old; and there were 26 eyes that were randomized in patients from 16 to 21. So a total of 33 eyes in the pediatric population.

Though these numbers are too small for any realistic statistical analysis, one can see that in the cross-linking group, there was an improvement of 4.4 diopters in these 15 patients from 66.4 diopters to 62 diopters. This compares to 11 patients in the control group where there was continued worsening and a steepening of the cornea of two diopters in patients less than 16, and, again, there were only 3 observed patients in this

group.

There was an improvement in these pediatric improvements of 1.6 diopters compared, again, only to 3 patients in the control group of continued progression of 2 diopters. So improvement in treatment group, worsening in control group.

So I think these efficacy results really represent an excellent outcome in patients after corneal collagen cross-linking.

Looking at pooled analysis of randomized eyes, there was a 2.6 diopter difference in the KC treated group versus the KC control group, indeed the treated group improving by 1.6 diopters on average, with a substantial number of patients improving their corneal topography.

When we looked at individual study results, UVX-001 and 002, these similarly corroborated pooled study results both met endpoint criteria with statistical significance.

So cross-linking really was effective in stopping disease progression over the one-year period of the treatment, and we saw improvements in

corneal topography compared to control and improvements in corneal topography when looking at the treatment group alone.

Remember, these are patients who had been worsening and, for the most part, are now getting better.

So let's shift gears and look at the studies of corneal ectasia after refractive surgery. In the pooled studies, there were a total of 179 eyes randomized between treatment and control; 84 percent completed the 12 months of the study; 16 percent were discontinued, again, a number of these because of the loss of one study site.

You can see here that the mean age, 43, was a little over 10 years older than patients with keratoconus, as might be expected, because patients with corneal ectasia who have had LASIK tended to get the LASIK later on in life.

Again, there was a male to female preponderance, and Kmax was similar initially between the two groups, 55.4 versus 54.8. And if you note here, these are somewhat lower than the

keratoconus cases where the average Kmax was in the 60s.

Looking at the timing of crossover as we did with the keratoconus subgroup, I turn your attention again simply to the lower row: 88 eyes were enrolled, 87 control eyes were available at 3 months; 48 crossed over after 6 months, leaving 32 control eyes, and 29 additional eyes crossed over between 6 and 12 months, leaving 2 observed control eyes.

Let's look at results. Again, this is the salient result of the ectasia group. In the treated group, there was .7 diopters of flattening compared to .7 diopters of steepening in the control group, again, a group that might expected to be progressive. This met the efficacy criteria of 1.0 diopters. The difference in the two groups was 1.4 diopters, meeting our definition of study success, and it was statistically significant.

Again, paralleling the keratoconus group, as one looks at healing after cross-linking, there is an improvement over time, .1 diopters to

.5 diopters to .7 diopters compared to the control group, where the efficacy criteria was met at 6 months with a difference of 1.1 diopters with statistical significance.

Observed eye analysis again corroborates this, showing continued improvement and a difference that meets the primary efficacy endpoint.

Finally, looking at an all-treated eye analysis of about 200 study eyes, we see the same thing. There is an improvement of .7 diopters looking at the ectasia group alone treated over the time course of one year.

Now, whereas the average change in this observed cohort of 74 patients was an improvement of .8 diopters, you can see here on the left side of the graph that 65 percent of eyes improved from their baseline corneal topography. Indeed, 20 percent improved by 2 diopters or more, similar to the improvement that we found in the keratoconus group. Three eyes continued to worsen by 2 diopters or more, and we'll discuss these a

little bit later on.

So looking at efficacy of ectasia, again, the results of the study meet the primary efficacy endpoint. These results are corroborated by the individual studies, UVX-001 and 003, and cross-linking again was effective in stopping disease progression in the ectasia subgroup over the course of one year.

Turning over to safety now. For the safety database, data was pooled over the three phase 3 studies. We evaluated the cross-linking group compared to the control group from baseline to 3 months, 205 eyes randomized in progressive keratoconus and 179 in corneal ectasia. And we evaluated eyes, all eyes, at 12 months, 293 KC eyes and 219 ectasia eyes.

Now, importantly, no subjects were discontinued because of an adverse event. The most common ocular adverse events that we as investigators observed from baseline to 3 months were typically expected sequelae of the corneal epithelial debridement and the subsequent healing.

And as we'll see, these occurred at a higher incidence in the treatment than in the control group. Remember, the control didn't have any epithelial debridement. They just looked at a light and their epithelium remained intact.

Here is a list of AEs that occurred greater than 10 percent at 3 months and accepting corneal haze and corneal striae. The others seemed to be AEs that are likely related to the de-epithelialization.

When we then looked at these patients at month 12, there were only a handful of adverse events. In progressive keratoconus, a handful of patients had some remaining corneal haze, 2, punctate keratitis, 2 with corneal scars. In ectasia, again, only 6 AEs, visual acuity reduced in 4 subjects, and corneal scar in 2 subjects.

One thing that we did look at was corneal haze. As we know, corneal stromal haze is an expected concomitant of the corneal collagen cross-linking procedure. Patients typically have a fine dust-like appearance to their cornea, which

evolves over time. It tends to be seen at month 1 and month 3, as you can see on these Scheimpflug images, and then dissipates over the time course of one year until the point, on average, patients returned to baseline at the year follow-up point.

Looking at serious adverse events, there were no deaths. There were a total of 7 SAEs. Five of these SAEs were non-ocular, 2 were in one patient with suicide attempts. This patient continued the cross-linking study and completed it. One had injury, appendicitis, and infectious cat bite. There were 2 ocular SAEs. So these are a little more important to look at.

The first SAE was a 19-year-old who developed an infectious corneal ulcer. This occurred and was diagnosed 3 days after the cross-inking. He was treated with antibiotics and corticosteroids, and the ulcer was reported resolved.

The second was in the ectasia study group, where there was an epithelial in-growth beneath the flap in a 47-year-old patient. This was reported

1 month after cross-linking. The investigator lifted the LASIK flap, removed the epithelial in-growth, and reported the SAE resolved.

Study centers also performed corneal endothelial cell counts with specular microscopy. First, turning your attention to the keratoconus group, they were similar, treatment and control, ECC initially.

Note the larger standard deviation that these patients have than typical patients because of the difficulty in getting a good specular microscopy on KC and ectasia patients.

There was a very small change from baseline at 3 months, a little loss in the treatment group, a little gain in the control group. If we extend the treatment group out to 12 months, there was a little gain at the end of the day in the keratoconus group.

If we now look at the ectasia group, again, similar initially. Both treatment and control lost about 2 percent of cells at the 3-month visit, as defined by the specular microscopy. We carry on

the treatment group. There was a loss of about 112 cells on average.

You can see here the fairly wide scatter that we have with these keratoconus and ectasia populations, again, probably secondary to the difficulty obtaining a good specular microscopy because of the irregular corneas and also the difficulty of getting speculars in one position, again, because of the irregular corneas.

Looking at the keratoconus group, it's a fairly Gaussian bell-shaped distribution, most patients remaining stable, and a number on each of the sides both gaining and decreasing cells by the cell count. Similar with the ectasia subgroup, you see the rather wide scatter. Again, this is likely secondary to the difficulty in obtaining maps from patient to patient time to time in these difficult to measure eyes.

We then looked at vision outcomes as a safety indicator to see if there was any substantial change in vision. Remember, the reason we're doing the cross-linking is to make the

corneal topography more stable, keep the corneal shape unchanged.

But looking at vision outcomes, first at best corrected vision, the blue line is the treatment group, on average, there was an approximately one Snellen line improvement of best corrected visual acuity after cross-linking, looking at the control group; and, again, there are not many that are seen at 6 and 12 months, but they tended to worsen over time.

Uncorrected vision had a similar appearance, approximately one Snellen line improvement in uncorrected vision in the treated keratoconus patients.

Now, again, a little easier to dissect this by looking at stratified results. The mean change was an improvement of about six letters on the ETDRS chart. About 25 percent of patients gained two or more Snellen lines of best corrected vision, and about 5 percent of patients, 5 eyes, lost two or more Snellen lines. The vast proportion of patients remained stable from the best corrected

viewpoint.

Looking at corneal ectasia, a similar pattern. There was a one Snellen line improvement on average in treated patients compared to some degradation in the control group. A similar appearance in uncorrected vision, an improvement of one Snellen line, a little aberrant point of just two control eyes that actually gained vision at the end.

Stratifying the ectasia subgroup, on average, they improved around 6 letters, much like the keratoconus group. Over 30 percent improved by 2 Snellen lines or more, and there were 3 eyes that lost 3 Snellen lines.

Looking at this loss of three Snellen lines, there was a transient reduction of best corrected vision at week 1, and this was in substantially higher proportion in the treatment subjects compared to the control subjects, as one might expect. These patients had epithelial defects and healing epithelial defects that might decrease their spectacle corrected vision.

As an aside, it's important when looking at keratoconus patients that spectacle corrected vision is not really the outcome indicator of greater importance. These patients typically are corrected with contact lenses.

The goal of cross-linking is to keep that topography stable so it doesn't become too irregular to not wear a contact lens or indeed to improve the topography so contact lens wear is easier and more beneficial to the patient.

Indeed, just anecdotally, from our own center, we've looked at contact lens patients, and 25 percent of patients who have come in for cross-linking on our clinical trials were contact lens tolerant, and at the end of the day, we were able to fit a vast majority of them with contact lenses.

So we don't know if cross-linking, per se, improves contact lens tolerance, but it certainly appears that patients do quite well afterwards.

So getting back to this slide, this transient reduction improved to equivalency

essentially between treatment and control at 1 month and 3 months.

At 12 months, there were four CXL eyes that lost three lines of best corrected vision, 1 in the keratoconus group, 3 in the ectasia group. We specifically looked at these, and there were no predictive preoperative characteristics. There was nothing that we could see on clinical exam or by history that explained this.

Patients were given visual function questionnaires. On these visual function surveys, which were graded on a scale of 1 to 5, 5 being the worst symptom, 1 being the least, you can see that on average, there was a small, yet meaningful improvement in patient visual function, including things like light sensitivity, double vision, fluctuation in vision, glare, and halo, those things typically complained about by the keratoconus population.

Similar findings were seen with corneal ectasia, with small, yet meaningful improvements in a number of these subjective visual function

indicators.

So when looking at safety, this study, these combined studies had a robust safety database for really what is an orphan indication, nearly 500, a little bit over 500 eyes in the safety database.

Collagen cross-linking was safe and certainly well tolerated by patients over the 12-month study period. There were only two ocular SAEs, both of which resolved. And most of the common SAEs, as you saw, were typically expected sequelae of the debridement of the cornea.

Corneal haze, as expected, as a concomitant of the cross-linking procedure was mild to moderate in intensity and resolved in most patients over time.

So if we look at the totality of what we have seen in these clinical trials, there is a very positive risk-benefit profile for collagen cross-linking in both corneal ectasia and keratoconus patients.

Cross-linking provided clinically meaningful and statistically significant improvement in

corneal curvature. So these patients who were getting worse preoperatively, in general, were getting better afterwards.

Cross-linking was effective in stopping disease progression, and it certainly was very safe and well tolerated. In fact, again, the treatment group improved in a patient population that left untreated would continue to progress.

Importantly, cross-linking slows or prevents disease progression and keeps patients in contact lens wear. If patients can retain their normal corneal configuration without getting worse, more than likely, they will be able to continue wearing contact lenses, hopefully over a lifetime.

Cross-linking would be the first drug-device combination in the United States for treatment of patients with these ectatic corneal diseases. Both are orphan indications. And as we all know, for our patients with KC and ectasia, there is a very much unmet clinical need for collagen cross-linking in the U.S. to treat patients with keratoconus and corneal ectasia. Thank you.

Sponsor Presentation - David Muller

DR. MULLER: Thank you, Peter. And I'm just going to finish with a brief survey.

In discussions with the FDA and I would say in the hopes of ultimate approval for our device and drug, we are proposing a phase 4 study to possibly answer any lingering questions that anyone might have.

We believe without a doubt that UVX-001, 002 and 003 have established the safety and efficacy of our drug and device through 12 months. Cross-linking literature that's available, you've heard a little bit, three-year literature, 10-year literature, that does suggest strongly and statistically significantly that there is persistence of effect.

So what we're proposing is a prospective observational single-arm study to collect approximately 500 study eyes to be enrolled with the goal of having at least 250 of those eyes evaluable at 36 months.

We will look at efficacy and determine

change from baseline of Kmax at 12, 24 and 36 months. On the safety side, we will look for AEs, slit lamp examinations, BSCVAs, pachymetry, tonometry, and endothelial cell counts to further add robust evidence to this procedure and the data set.

I think in conclusion, you've heard from Dr. Rajpal about the medical need. I think you've heard from Dr. Peter Hersh on the medical safety and efficacy. And I think, as we all know, we're dealing with a disease that currently has no treatment. Progressive keratoconus and corneal ectasia lead to vision loss, often ultimately lead to corneal transplant.

The cross-linking now is performed internationally for over a decade. Hundreds of thousands of patients have been treated. Our system alone in several hundred sites around the world have treated over 75,000 patients for these indications. The drug substances and drug products that we are proposing to be approved are manufactured under the most strict conditions in

FDA-monitored sites, both device and the drug.

This is orphan population, a population who is, I would say, desperately waiting for this solution. And I think we need an approved labeling guide for both physicians and patients. I think because of the nature of so much cross-linking outside the U.S. and some that has come to the U.S., there is confusion as to what really works.

What you've seen here is really the only full-on study that can statistically tell you what works, and I think providing the physician with the opportunity to treat their patients and provide the patients with clear indication of where they should be going for treatment.

So again, the totality of the safety and efficacy I believe is supported by our study, and we are seeking approval for corneal collagen cross-linking for the treatment of keratoconus and ectasia, and we hope that our data supports that, in your opinion. Thank you very much.

Clarifying Questions

DR. AWDEH: Okay. I would like to now move

on to clarifying questions for the sponsor. In order to do this in an orderly fashion, I'd like to go through the order of presentation the way the sponsor did.

So before you ask a question, please state your name verbally into the record. And I'd like to start with questions regarding disease background and mechanism of action or unmet need for Dr. Rajpal.

DR. HUANG: I would like to ask the sponsor to clarify the concentration of the medication using the study. I was a little bit confused by the accompanying report. It varies from 0.1 percent to 0.12 percent.

DR. MULLER: The drug that we're looking to have approved is at .12 percent. There is a natural variation in the percent of riboflavin because it is a mixed chemical. But during the range of the study, in the study that was presented, the average was .12 percent. And so when we formulated our drug, made in the GCP facility, it was chosen as .12.

Essentially, that difference in riboflavin makes no difference in the cross-linking because the dose really that's causing the effect is the UV dose. And so something in the second or third decimal point of the actual riboflavin really doesn't make a difference. It's only an energy transfer agent.

DR. AWDEH: Cynthia Owsley, do you have a question? No. Okay.

Are there any other questions regarding the device and drug description for David? Go ahead.

DR. LEGUIRE: Larry Leguire. I need clarification on CC-93 and 94 slides. What is the Y-axis? Is that probability? What is the Y-axis?

DR. HERSH: Peter Hersh. CC-93 and 94 show results taken from subjective patient questionnaires. So patients received a questionnaire, grade your light sensitivity on a scale of 1 to 5, 5 being the worst. And we would take that number preoperatively and that number at 12 months, and the difference, the average is what you see here.

DR. LEGUIRE: Thank you very much. Another question is on your crossover, you know that at 6 months, a number of patients do cross over. Yet, at least in the control group, there are 78 that you do have 6-month data from.

What I would like to see is data from your patients where you just take the patients that actually have real data at 6 months, and compare their data to baseline for both groups; that is, getting rid of all this carry-forward data, you should have enough then at least at 6 months to tell us what those patients have done at 6 months versus at baseline, control as well as the treated group.

DR. HERSH: Could we look at the observed data slide from the keratoconus group, please? So these are observed eyes in the randomized clinical trial. The numbers are as written. So there are 96 eyes at 3 months, 95 at 6, and 89 at 12 in the treated keratoconus group. There are 96 observed control eyes at 3 months, 39 at 6 months, and only 2 at 12 months.

So here you can see, looking at observed real data, the control group worsened and the treatment group got better, with a significant difference of 2.3 diopters.

DR. LEGUIRE: Okay. Thank you for that clarification.

DR. BELIN: Can you clarify how many of your patients in the control group into the crossover -- in other words, how many opted to have their first eye treated after being in the control arm?

DR. HERSH: I think we have that slide available. If you look just at the last line, there were 103 randomized to control. At 3 months, 101 still remained. Fifty-seven crossed over after 3 months. So that left us with 39 control eyes. Thirty-three of the remaining crossed over, so 90 eyes crossed over from their control group.

DR. BELIN: So 90 eyes out of the original 102 opted to be treated.

DR. HERSH: That's correct.

DR. BELIN: How many of the original treated

eyes opted to have their second eye done? That's not stated.

DR. HERSH: I believe it's around 50 percent of fellow eyes that were treated.

DR. BELIN: Is there a rationale for the discrepancy between those who have received treatment for half of them opting not to have the second eye being done versus those who have not been treated having almost 90 percent deciding to have something done?

DR. HERSH: Typically, treating the second eye was done on the basis of eligibility for the study. As we all know, keratoconus can be markedly asymmetric. So either the second eye that was not treated did not meet study criteria or the second eye was deemed at that point good enough that they didn't elect to have it treated.

DR. BELIN: Okay. That seems a little odd. If you look at the controls and if you randomly selected eyes -- that just statistically doesn't seem correct.

DR. HERSH: Well, the eye that was

randomized was preselected by the investigator. So a patient would come in. Typically, we picked the bad eye, and that eye would be randomized.

DR. BELIN: If you look at your average, if you're using Kmax, your actual average Kmax on your control was a tiny bit higher than in your treated.

DR. HERSH: Yes.

DR. BELIN: That also doesn't seem to make sense.

DR. AWDEH: Dr. Sugar?

DR. SUGAR: Joel Sugar. I don't know if this is in sequence or not. But the question about the protocol, in terms of the eyes that had 400 microns or less than 400 microns after epithelial removal and were treated with the non-dextran-containing riboflavin, was the corneal thickness measured subsequently during the treatment, and what was the corneal thickness at the end of the treatment?

Then a follow-up to that is were the endothelial cell count data substratified to the patients who had the non-dextran-containing

riboflavin compared to those who had the viscous riboflavin?

DR. HERSH: Peter Hersh again. In the endothelial cell count data, the results were not stratified comparing those that were swelled and those that were not swelled.

DR. SUGAR: And was the pachymetry measured during the treatment in those who were swelled in order to reach the 400 microns?

DR. HERSH: In the clinical trial, it was not. We would measure with ultrasonic pachymetry before ultraviolet exposure, but we did not have on protocol to measure afterwards, no.

DR. MacRAE: I have a question. Scott MacRae. So when you did the 400 micron measurement, were you measuring over the central cornea or over the thinnest part of the cornea?

DR. HERSH: We were looking for the thinnest part of the cornea. Several measurements would be taken -- five measurements were taken looking for the thinnest spot at each of the pachymetry measurements.

DR. AWDEH: Dr. Feman?

DR. FEMAN: I'm Steve Feman. There were a couple of slides that you presented that were unique. Particularly, could we look up slide number 90, CC-90? And you see there are just two patients there, but two patients obviously in the sham group got substantially better.

Can you account for that?

DR. HERSH: You can't really account for it. There is a lot of variation when measuring visual acuity and keratoconus and ectasia eyes because of their irregular corneas. So I think these two eyes had better vision at that time, but we can't account for it by any real clinical examination of those patients.

DR. FEMAN: So essentially the sham patients -- those sham patients improved better than the treated patients. And those are patients that never got a secondary treatment 3 months later or 6 months later. They were completely untreated. The two that had no re-treatment other than having had the riboflavin drops put in their eyes.

DR. HERSH: Right. But these are only two patients. You can see there's no statistical significance at all.

DR. FEMAN: Well, you had no other patients that were controls at that level. All of the other controls apparently had been treated.

DR. HERSH: Remember, when we're looking at these outcomes, the important outcome that we're really looking for is stabilization of the cornea and maintenance of their corneal topography. Patients with keratoconus or ectasia typically have varying visions and typically wear contact lenses to get their best corrected vision.

So the real outcome indicator that is important in cross-linking is stabilization and maintenance of that corneal topography.

DR. FEMAN: Thank you. I thought that the outcome was vision.

DR. HERSH: No. The primary outcome that we're looking is stabilization of corneal topography, is improvement in corneal topography compared to the control group.

DR. AWDEH: Dr. Huang?

DR. HUANG: This is Andrew Huang. This is a continuation of Dr. Sugar's question. In the sponsor's report, you have a very nice calculation talking about the pharmacokinetics of using the topical riboflavin in the cornea thicker than 400 microns. So technically you need to deliver about 16 drops over the course of 30 minutes.

But in the cornea thinner than 400 microns, in the protocol, you need to use the so-called riboflavin with dextran to use every 10 seconds over 2 minutes until you've reached 400 microns.

So theoretically, you will be delivering twice or even more of the concentration to the cornea.

So the first question is, is there any subgroup analysis in terms of the pharmacokinetics in those groups? Do they get additional reactive oxygen species that cause further corneal steepening?

Second, in this subgroup, is there any analysis in the endothelial density -- because the

cornea is thinner and you get twice or more of the dosage of the riboflavin, do they have any endothelial damage?

DR. MULLER: This is David Muller. So in the addition of extra riboflavin, start with the dextran and then move on to the saline-based, the concentration is exactly the same in both. So by adding more riboflavin -- the riboflavin, when it enters the cornea, is continually diffusing through the cornea, basically going into the aqueous.

So the concentration could never become above .12. When you add two .12 solutions, you end up with a .12 solution. So it's really always diffusing through it, and you could never increase the concentration above that because basically the bio-diffusion doesn't let that happen.

So you're really dealing with the UV dose under the riboflavin.

DR. HUANG: But your endpoint is to achieve the flare in the anterior chamber. So obviously, you want to achieve a much more higher flare in the anterior chamber in order to start the treatment.

So I don't agree with your calculation that using the same concentration over a course of different drugs, there is no systemic side effect or similar systemic side effect.

DR. MULLER: I have to disagree. It could never become above .12. It is physically impossible to take two .12 solutions and end up with a .24 solution.

So certainly there's more concentration in the posterior cornea, and you'll see the flare come in. But it could never become above .12 in the anterior cornea where we're actually doing the treatment. It can't happen. It just can't happen.

DR. HUANG: If that were the situation, then why don't we just soak the eye for 20 minutes or 10 minutes rather than using the drops every 2 minutes?

DR. MULLER: In fact, outside the U.S., that's typically now what is actually happening. The protocol, the treatment that we're seeking approval for, was the original Dresden protocol that looked for a half-hour of treatment. But your

point is correct.

DR. HUANG: I don't mean to disagree with you, but I think according to Dr. Hafezi's study, they have changed various parameters using the same concentration, but different irradiation time to achieve the efficacy, and that is understandable. But I don't think the drops itself can be treated lightly. You say, well, you're using 1 drop is equivalent to 2 drops.

DR. MULLER: Well, I won't discuss Dr. Hafezi's work because it's observational and not statistical. But I would say that, again, the basic physics, if I have a .12 solution in one hand and a .12 in the other hand, I could mix them all day long and never get a .24 solution. They will always be a .12 solution.

DR. HUANG: Yes. That's by concentration, but that's not net accumulation.

Also, when you use the first drops, it's the dextran. So that has a better retention time. The second drops is really a hypotonic solution, and that has a much better penetration because the

whole idea is the cause of the cornea swelling.

DR. MULLER: That's, again, correct. But again, if you put two .12 solutions with riboflavin, with dextran, and with water in the cornea, it will always be at .12. Otherwise, you would be able to make the perpetual --

DR. HUANG: I'm not arguing the concentration. You can put 10 liters of .12 and all the 10 liters of .12 together is still .12. I understand that. But the problem is 10 liters of .12 is different than 1 liter of .12, the net effect.

DR. MULLER: I guess I would humbly disagree, because the effect is the UV on the riboflavin. So the UV effect on .12 percent riboflavin will always be the same.

DR. AWDEH: Dr. McLeod?

DR. McLEOD: Stephen McLeod, UCSF. I just had a question I think for Dr. Hersh about the protocol and the interaction between your enrollment criteria and the crossover strategy, and the specific question I have is this.

Your criteria, as I understand it, requires demonstration of progression over time, which means you would have patients who were seen at one point in time, they are re-measured, they're showing an increase in the Kmax, then they're enrolled.

One might bring to question the fact that these are intrinsically very noisy measurements, and so obviously we have the potential for regression to the mean phenomenon once you start studying these patients.

If you allow patients to switch over at any point after 3 months, given the fact that one would imagine that it is patients who are showing progression who would then switch over, leaving the others un-switched, who could then switch over later on once they show progression, how do you extract regression to the mean phenomenon from what we're seeing in the data or how did you think about that in your study design?

DR. HERSH: As we saw, most patients crossed over, leaving on two at the end of the day. Typically, the crossover was secondary and impelled

by patient convenience.

One of the reasons I think the original 3-month crossover date was chosen was even back when we started this in 2007, keratoconus patients knew about cross-linking. Cross-linking was still being widely used internationally with great success.

So simply recruiting patients into a study like that without their ability to cross over would have been difficult. So patients entered the study really explicitly to have cross-linking, knowing that they were going to be cross-linked, knowing that their eye that was randomized to control could be crossed over.

So it was almost implicit in their entering the study that they were going to cross over because they entered the study in order to have cross-linking.

DR. AWDEH: Dr. Weiss?

DR. WEISS: Two questions. A question, first, the inclusion criteria. For the demonstration of disease progression -- and I'm

looking at slide 43 -- did you have to meet all of the criteria or just one of the criteria?

DR. HERSH: Peter Hersh. We just needed to meet one of the criteria for progression.

DR. WEISS: So with that in mind, the criteria of a myopic shift of greater or equal to .5 diopters, I teach my residents that that is the variability between two observers doing a subjective refraction on a patient.

So I'm curious what percentage of patients who were enrolled to meet the progression criteria had that as their only entry point. That would make me wonder personally if it was only .5 diopters, if indeed they actually progressive keratoconus.

DR. HERSH: We had to meet one of these criteria. I don't think we have that data on hand.

DR. WEISS: Okay. So with that in mind, a follow-up question is with looking at the visual improvement. I understand the primary endpoint is the Kmax, but my impression from reading the briefing package was there was a large amount of

emphasis that visual acuity improved.

Consequently, it seems that that was an important result, from the sponsor's standpoint, of the study.

So when I look at table 14, which was on page 62, it showed me that at all time points, the control group also had an improvement of vision except for month 6. So it makes me wonder about were these progressive keratoconus and because these were subjective reports of vision from a patient, who can go up a couple of letters in one visit and down a couple of letters in another visit, what is really the significance of the vision improvement or decrease. Can we even use that, because how would one explain how an untreated group has an improvement of vision, as well?

Of the briefing package, I'm looking at page 62, and it was table 14. Now, the summary in the sponsor's briefing package showed the one time point where the control group decreased vision, but it didn't mention all the other time points where

their vision actually improved.

DR. HERSH: Here, if you look at the 6-month data, where we have a substantial number in the control group and a substantial number in the treatment group, there was a 5.8 letter increase in the treatment group compared to a 1.1 increase in the control group.

DR. WEISS: So what does the increase in vision mean if the control group, which theoretically or stated to have progressive keratoconus, is improving without treatment?

DR. HERSH: Well, I certainly agree with you that there is variation in corrected visual -- in uncorrected and best corrected vision in these patients. I think there's probably some training effect because they're looking at ETDRS charts. Clearly there's variability from time to time.

These patients have a lot of aberrations, and their Snellen visual acuity really isn't an appropriate measurement of their visual quality. We're really looking at vision as a secondary outcome indicator, more as a safety indicator. And

there was nothing that we could see from a safety point of view that influenced spectacle or uncorrected vision.

DR. WEISS: So I guess I hear the sponsor distancing themselves from the reliability of using vision postoperatively, and I would contend that if it's not reliable in the control group, it may not be reliable in the treated group.

The last question I had was table 43, page 129 of ocular adverse events. I want to understand in terms of looking at the SAE percentages -- so the control group that subsequently got cross-linking also had their own set of ocular adverse events. But the statistics that are being presented here, as I understand it and I would like to be corrected if my understanding is off, is only looking at the cross-linked group.

So it doesn't pool everyone who got cross-linked from the initial cross-linking group versus the control people that got cross-linked. It's only looking at the initial cross-linking

group. Is that correct?

DR. HERSH: The safety database were all eyes.

DR. WEISS: Okay. So whether you were part of the initial group or whether you --

DR. HERSH: Correct.

DR. WEISS: -- were part of the subsequent group, you got put --

DR. HERSH: It's everybody who got a cross-linking treatment in any eye.

DR. WEISS: Got it. Okay. I guess I'll throw in one last question. It looks like the ectatic group didn't get as much effect as the progressive keratoconus group. Is there any thoughts on why?

DR. HERSH: We don't know exactly why, but there are a few possibilities. First, you're dealing with an older age group. And we know that older patients with keratoconus and possibly ectasia tend not to be as progressive.

Secondly, the baseline Kmax in ectasia was about 10 diopters less than in keratoconus, and

there seems to be a more robust improvement effect in patients who have worse degrees of disease.

Finally, it may be something to do with also cone location. Ectasia patients tend to have a lower cone, and we find that more centralized cones may have a more robust topography improvement effect.

DR. AWDEH: Dr. Leguire? Dr. Belin?

DR. BELIN: A couple comments. One, I want to just further comment on what Stephen said about Kmax. Kmax is a very noisy parameter. It's also more noisy and more peripheral to your cone. It's also not very reproducible and clearly is not indicative of progressive disease.

The protocol called for topography, tomography, meaning Scheimpflug, and OPD, and the only parameter that's being reported is Kmax. You may have a stable Kmax and have progressive ectasia on the posterior surface. We have no idea.

So I would ask us not to call this progressive disease. We don't know if it's progressive disease, and a lowering of Kmax by a

diopter does not mean you stabilize the disease. It means you've lowered Kmax.

Kmax is not a global parameter of curvature. So the comment that we improve curvature cannot be told. You've changed Kmax. As I said, Kmax will vary on cone location, also.

The other parameter about progressive disease -- and you don't have put the slide; I'm just reading off of the handout -- was increase of greater than 1 diopter. In the handout, it says regular astigmatism. I assume that's a typo, because normally we don't have regular astigmatism in keratoconus.

I agree with Jayne that a myopic shift of a half-diopter is within noise levels

The other comment here is a decrease in greater than 0.1 millimeters in back optical zone radius in rigid contact lens wearers. Unless you've kept your diameter of your lens constant, a change in back curvature is meaningless because your vault is a combination of back curvature and diameter.

So for me, none of these parameters really are good indicators of progressive disease. I have no problem calling these people keratoconus in their 60s, but to say they're progressive I think is pushing it. And to say that the results show a halting of progression I think is really pushing it.

I'm also concerned with the question I had before of the lack of the amount of patients who had one eye treated opting to have their second eye treated, especially in light of the follow-up answer that these patients -- I think you just said these patients came to the study expecting to be treated.

I also noticed in the data that there's no -- unless I'm wrong, there's no data on the eyes that were opted to be treated who were control. So we have no data on those, which suggests that those patients didn't have to meet the same criteria to have the open label done.

So I'm still concerned that we have really a majority of patients who have had one eye treated

who opted not to have the second eye treated.

Those are my comments.

DR. HERSH: Peter Hersh. Just to clarify regarding the second eye. Somewhere between 50 and 75 percent of eyes crossed over. And in order for the fellow eye to be treated, it needed to meet the study criteria. And I don't know the exact number, but a large number of those eyes did not meet the study criteria to have their second eye treated. Typically, their Kmax wasn't high enough.

DR. AWDEH: I have a follow-up question for the sponsor regarding Dr. Belin's comment. Can you comment on the protocol of obtaining corneal topography in these patients? Specifically, was their training involved to the technicians who performed the corneal topography?

Were artificial tears used or not in obtaining these corneal topographies, and was more than one measurement obtained from these patients at the time of obtaining corneal topography?

DR. HERSH: Peter Hersh. Regarding corneal topography, all study sites needed to have the same

equipment, the Pentacam HR. There was a specific software that was used amongst study sites.

There was training of technicians regarding obtaining the Pentacam. All study centers were observed during their first days of treatment by the sponsor. Only one Pentacam typically was taken, and they were done in the controlled fashion that was specified by the sponsor at the time.

No artificial tears were used.

DR. AWDEH: Okay. All right. Dr. Owsley?

DR. OWSLEY: Cynthia Owsley. From your briefing document, my understanding is you used the RSVP questionnaire. I just have some questions about that.

What percentage of each group received the questionnaire? I believe you gave it at screening, not at baseline. And what percentage actually completed the questionnaire at the 12-month follow-up?

DR. HERSH: We have that information, but need to compile it for you. So I'll get back to you after the break, please.

DR. OWSLEY: Okay. Then on follow-up, looking at missing data, I guess the initial question would be was the questionnaire interviewer-administered or patient-administered, self-administered?

DR. HERSH: It was self-administered.

DR. OWSLEY: One thing with self-administration of questionnaires is that missing data, people skip items even if they're on the questionnaire and they're asked to complete the questionnaire. So I'd be interested in the missing data rates.

Then as you're looking at this data, if you're going to comment later, I'm wondering what was the loss to follow-up on the questionnaire data. In particular, in slides CC-93 and 94, patients only appear in the graph that completed the questionnaire at both the baseline and the -- I guess looking at your protocol, it appears it was done at screening and then at 12-month follow-up.

My final question -- I guess you could look at that later. But my final question is were these

differences statistically significant. There's no error bars and typically in questionnaires, there's a fair amount of variability in responses across patients who have these types of conditions.

DR. HERSH: We'll try to get all that for you after the break. Thank you.

DR. OWSLEY: Thank you.

DR. AWDEH: Dr. Feman?

DR. FEMAN: This is Dr. Feman again. I don't know who it's appropriate to address in the presentation, but you talked earlier about a number of fellow eyes that were treated, the eyes, or initially the sham portion of the study.

The 3-month data, for example, statistically there's no really significant difference between the two. So essentially you were doing this investigative treatment on an eye, the fellow eye, that you had no rationale to treat since you had no evidence at that time that there'd be any benefit in this treatment.

Particularly, for example, in the children, you had like 33 or so people under 21 years of age

that you treated. And how could you treat the fellow eye on a person that has a disease in one eye when you have no evidence, statistically valid evidence, at 3 months or at 6 months that the treatment was better than no treatment at all?

DR. HERSH: At the time of the treatment, there was a substantial amount of international data looking at the results of cross-linking, suggesting that it was effective. Therefore, patients, again, entered the study to have treatment. And based on what we knew from published results overseas, it was felt appropriate and indeed important to treat those eyes.

DR. FEMAN: Before you leave. Did an institutional review board that looked over your study approve the treatment of the fellow eye, the eyes that were considered the sham treatment, to get the investigative procedure?

DR. HERSH: Yes. The protocol was IRB approved.

DR. FEMAN: I understand that for the protocol. I'm talking about treating the sham eyes

to get treatment. Was that IRB approved? Did you go back to the institutional review boards and ask their approval to treat the sham-treated eyes with the investigation?

DR. MULLER: The crossover treatment, first of all -- it's probably worth mentioning, it was the prior sponsor that conducted that part of the study. But that was part of the FDA-approved protocol and was within the IRB that the patients could cross at 3 months. So it was all properly done.

DR. FEMAN: Thank you.

DR. AWDEH: Dr. MacRae?

DR. MacRAE: Just a quick question on the endothelial or a suggestion, and that is that you take your endothelial cell count data for the patients that were treated initially in your treatment group and just look at that group solely out to 12 months so that you're comparing apples to apples.

Then I think it's a good idea, the suggestion of taking the under 400 micron group and

just stratifying that. It would be helpful to look at that a little bit more carefully.

But from my perspective, I've done a lot of endothelial work. The endothelial data looks fairly reasonable. And from the international data, we don't see really a lot of indication that there's problems with that. But I'd be curious about the under 400 micron group and stratify that.

DR. HERSH: We can certainly look at that for you. But we did do some analyses. We found there was no difference or relationship between their baseliner Kmax and ultimately endothelial outcome. There was no relationship between their baseline pachymetry and their ultimate specular microscopy outcome.

So thinner corneas, thicker corneas, there was no relationship between either gain or loss of cells.

DR. AWDEH: Okay. We have one last question, and then we'll take a break. Dr. Weiss?

DR. WEISS: So the sponsor is asking for approval of the KXL device, but all the data that

we're seeing is the UVX. So we have no data on the KXL.

So I'm particularly interested, if 75,000 procedures have been done internationally, do you have any results in terms of particularly long-term stability? Because we have a changing amount of effect from 3 months to 6 months to 12 months.

When does this stabilize or does it wear off? And do you have any information from the 75,000 patients who have been treated outside the United States?

DR. MULLER: There are certainly a number of publications that individual clinicians produce outside the U.S. using our system. They use it with variable parameters, not necessarily the parameters that we are using here.

I think the thing to focus on, I think, as to equivalence simply comes down to really the dosage, and that is the dosage that's provided to the patient, 5.4 joules per square centimeter, with an average of three milliwatts across the beam, is identical between the two devices. It's really the

business end of the device.

So there's not a hair's breadth between what the UVX device delivers and what our device delivers.

DR. WEISS: So if you can humor me, those 75,000, I still think the data is important because it speaks to the machine, maybe not the actual dosage. So I'm sure you're familiar with the literature of what that has shown. So can you quote me your best study that someone' s reported, maybe the most long-term study with the most number of patients? When did it stabilize or is there no long-term study on it?

DR. MULLER: It's a little apples to oranges in that outside the U.S., most of the patients are being treated with what's known as the accelerated protocol. And in that case, there are -- and we might be able to find them at the break -- there are comparative publications looking at the original Dresden protocol, the accelerated protocol, and find them to give equivalent results.

So we are seeing the same stabilization as

we see here, but, again, it is a little apples to oranges.

DR. WEISS: I said I would make this short, but you're making it difficult for me. What is the date of stabilization? How long have they followed them out for? Has anyone followed them for two years? What is the longest they've followed them, and at what point do you get the same Kmax from one time point to another?

We don't have a stabilization in the study provided here. It keeps on changing at each time point.

DR. MULLER: It basically follows the -- and, again, I could try to find the publications at the break, but it follows the identical time course, but you have to -- it does follow the same time course, but it is a slightly different procedure because it's the accelerated protocol.

DR. WEISS: So in deference to everyone who needs a break and wants a break, maybe you could find an article to show us, and that would be

helpful for stabilization.

DR. MULLER: I think we'll be able to find that easily over the break.

DR. AWDEH: We will now take a 10-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume at 10:23 a.m.

(Whereupon, a recess was taken.)

DR. AWDEH: In the interest of time, we're going to move forward. We will now proceed with the FDA presentation.

FDA Presentation - William Boyd

DR. BOYD: Good morning still. My name is William Boyd. I'm the clinical team leader in the Division of Transplant and Ophthalmology Products.

Quite a few of my slides have already been covered, so I'm not going to repeat a great deal of this. Avedro submitted a new drug application, NDA-203324, for a combination product. And the proposed indications are the treatment of progressive keratoconus and the treatment of

corneal ectasia following refractive surgery. And the treatment uses Photrexa Viscous with dextran and Photrexa without dextran in certain patients and the KXL system for corneal collagen cross-linking.

We've already discussed that keratoconus is a condition characterized by progressive thinning and protrusion of the cornea, and there is potential loss of visual acuity.

Corneal ectasia is a complication following some refractive surgical procedures. It's also characterized by progressive thinning and protrusion of the cornea and potential loss of visual acuity.

The goal of cross-linking of collagens is to biomechanically strengthen the cornea. The cross-linking occurs in the presence of riboflavin with UVA exposure. And most of these other points have already been covered.

We've also already discussed the two riboflavin ophthalmic solutions. The Photrexa Viscous is a clear yellow solution containing the

.12 percent riboflavin phosphate sodium and 20 percent dextran. Photrexa, unlike Photrexa Viscous, does not contain the dextran component.

At this point, I'll turn things over to my CDRH colleague, Maryam Mokhtarzadeh, to discuss the device constituent.

FDA Presentation - Maryam Mokhtarzadeh

DR. MOKHTARZADEH: Good morning, distinguished advisory committee members, Avedro representatives, FDA staff, and the public. The combination product presented today includes drug and device components. CDER is leading the review of this application and CDRH consulting. As such, I will be presenting to you this morning the device description and related issues for this NDA.

The KXL system is a portable electronic medical device with an articulating arm to allow movement of the system for alignment of the UV beam to the patient's cornea. An internal battery powers the system. A radio frequency identification, or RFID, activation card is used to start the treatment.

Alignment lasers are used to aid the user in focusing the beam on the patient's cornea. UVA flux and irradiation time are controlled by an onboard computer system.

The KXL system delivers ultraviolet-A light at a 365 nanometer wavelength in a circular pattern onto the cornea after application of the drug component.

Software lockout ensures that the maximum allowable treatment parameters will be limited to 3 milliwatts per centimeter squared for 30 minutes and a maximum energy density of 5.4 joules per centimeter squared. The user will not be able to change the induction, power, and treatment time.

The RFID is preprogrammed with the system's parameters. The induction period is 30 minutes. UV total energy is 5.4 joules per centimeter squared, and UV irradiance 3 milliwatts per centimeter squared. Treatment settings are entered using a touch screen user interface, and the RFID card will only allow the above parameters.

Preclinical review of the KXL system

included evaluation of optical engineering and software. In particular, UV beam homogeneity testing was performed and met the predetermined acceptance criteria.

The software requirements and development environment were reviewed in addition to the software lockout described on the prior slide. Also, ongoing preclinical evaluation includes electromagnetic compatibility, or EMC, and electrical safety.

While the KXL system is the device proposed for marketing, all clinical data submitted in this NDA was obtained in studies using a different device, the UVX. The applicant provided a comparison between the two devices. Both devices are non-contacting UV light sources utilizing light-emitting diodes, or LEDs, to deliver UV light at a wavelength of 365 nanometers.

However, there are numerous differences between the UV device studied and the one proposed for marketing. A comprehensive list of differences appears in table 5 on page 13 of FDA's briefing

document.

Among many differences between the UVX system studied and the KXL system proposed to be marketed, which are listed in FDA's backgrounder, we note the following. First, the dimensions are very different. The KXL system is much larger and heavier than the UVX system.

The UVX system requires mounting on a tabletop stand by the user, while the KXL system is a standalone system on an independent wheeled console.

The UVX has the capability to be rotated and, therefore, to allow horizontal UV delivery to treat submits in a sitting or supine position, while the KXL system limits the patient position to the supine position.

The UVX system had three available beam diameters for investigators to choose between, 7.5 millimeters, 9.5 millimeters, and 11.5 millimeters, while the KXL system only includes a 9-millimeter fixed diameter. These will be discussed in greater detail on the next slide.

Finally, for the UVX system, UV focal alignment was subjective. The user observed the riboflavin fluorescence to gauge beam shape to determine proper alignment. For the KXL system, the alignment is objective. Two visible aiming lasers provide direct alignment confirmation in X, Y and Z directions, as will be discussed on a later slide.

While the protocol-directed investigators to select the correct illumination diameter setting based on the size of the eye, when asked how investigators were instructed to choose the appropriate illumination diameter for use, the applicant provided additional information stating that as part of site startup and training, investigators were instructed to select the medium aperture setting prior to irradiation based upon ease of alignment over the clear cornea and centration to the limbus diameter.

Of subjects who were cross-linked in the intent-to-treat population, according to the applicant, no subjects received the small diameter,

which was 7.5 millimeters. All UVX-001 subjects received the medium diameter, which was 9.5 millimeters.

As listed in this table, 10 subjects in the UVX-002 study received the large or 11.5 millimeter diameter, while 61 subjects are identified to have received the medium diameter. Seven subjects in the UVX-003 study received a large or 11.5 millimeter diameter, while 56 subjects are identified to have received the medium diameter.

While the majority of subjects in the clinical studies were treated with the medium or 9.5 millimeter setting of the UVX system, please note that no subjects studied were treated with an illumination diameter less than 9.5 millimeters, while the device proposed for marketing would only include a 9-millimeter illumination diameter. Therefore, use of the KXL system would result in a smaller corneal diameter treated.

With respect to another difference between the devices, for UV focal alignment, the UVX device studied used a subjective focal alignment. The

user observed the riboflavin fluorescence to gauge beam shape to determine proper alignment. For the KXL system to be marketed, the alignment is objective. Two visible aiming lasers provide direct alignment confirmation in X, Y and Z directions, as seen on the image on this slide.

Therefore, we note that not only is there a difference in the method of alignment, i.e., subjective or objective and the related usability issues, but there potentially could be a difference in the targeted focal plane due to the fact that the KXL system alignment method occurs independent of riboflavin diffusion.

Therefore, while an objective method may improve consistency of the plane at which treatment is delivered, it is unclear how that treatment plane may differ from the ones studied and the resulting impact on safety and effectiveness.

The panel will be asked to discuss the following. The studies were conducted on a different device, the UVX, than the one proposed to be marketed, the KXL system. Differences include,

but are not limited to, illumination diameter and UV focal alignment.

In light of the differences and lack of any data collected using the KXL system, please discuss the adequacy of the current data set to assess safety and efficacy of the KXL system.

I will now turn the presentation back over to my colleague, Dr. Boyd.

FDA Presentation - William Boyd

DR. BOYD: William Boyd again. And again, most of what I'm about to present has already been presented, so I will just touch briefly on it.

Regarding the cross-linking procedure proposed for marketing, it's already been discussed that using topical anesthesia, the epithelium is debrided using a standard aseptic technique. And after that debridement, one drop of Photrexa Viscous is instilled topically on the eye every 2 minutes for 30 minutes.

At the end of that 30-minute soaking period, the eye is examined under the slit lamp for the presence of a yellow flare in the anterior chamber.

And if the flare is not detected, a drop of Photrexa Viscous is instilled every 2 minutes for an additional 2 to 3 drops, and then the eye is rechecked, and this process can be repeated.

One the yellow flare is observed, ultrasound pachymetry is performed. If the corneal thickness is less than 400 microns as measured by an ultrasound pachymeter, 2 drops of Photrexa are instilled every 5 to 10 seconds until the corneal thickness increases to at least 400 microns.

At this point, the eye is irradiated for 30 minutes at 3 milliwatts per centimeter squared using the KXL system, as per its instructions. And during irradiation, there's continued topical instillation of 1 drop of Photrexa Viscous onto the eye every 2 minutes for the 30-minute irradiation period.

On to clinical studies. We've already discussed that progressive keratoconus involved two studies, 001 and 002, and corneal ectasia following refractive surgery involved two studies, 001 and 003. 001 was a single-center study and 002 and 003

were multicenter studies, and all of the sites were located in the United States.

As part of the phase 3 trial design, only one eye was designated a study eye. The study eye was randomized to either corneal cross-linking or sham group at day zero at a 1 to 1 ratio. The main inclusion criteria for the corneal ectasia studies were diagnosis of corneal ectasia after refractive corneal surgery; for example, after LASIK or PRK.

The main inclusion criteria for the keratoconus studies were progressive keratoconus defined as one or more of the following changes over a period of 24 months or less before randomization. And I won't list these again, but we've already discussed these four.

There were no exclusions in the inclusion/exclusion criteria for prior corneal cross-linking, no exclusions for Intacs in post-refractive corneal ectasia population, and no exclusions for subjects with a history of multiple refractive procedures.

A discussion question that you'll be asked

to address later, the applicant proposes the indication of progressive keratoconus. Please discuss the applicability of extrapolation to the general keratoconus population.

Again, for phase 3 trial design, the corneal cross-linking group received the corneal cross-linking procedure at day zero. Subjects in the control or sham treatment group had topical anesthetic administered. They did not have their corneal epithelium removed. They had either Photrexa Viscous or Photrexa administered, and the UV-A light source was placed in front of the eye, but it was not turned on.

Regarding the control sham eye, at month 3 or later, control sham subjects were given the option of having corneal cross-linking performed on their controls study eye. After treatment, these eyes were followed for 12 months according to the same schedule and protocol as the study eye in the original corneal cross-linking group.

Regarding fellow eyes, again, at month 3 or later, all of the patients in the corneal

cross-linking group and the control group had the option to have the corneal cross-linking procedure performed on their fellow eye, which was the non-study eye.

After treatment, these eyes were also followed for 12 months according to the same schedule and protocol as the study eye in the original corneal cross-linking group, and the outcomes for these eyes are not presented.

This is the schedule of visits and procedures. A very busy slide, but I'll just point out that there's a screening visit, the treatment visit, post-treatment visits at day 1, week 1, month 1, month 3, month 6, and month 12.

At this point, I'll turn over the efficacy discussion to my statistical colleague, Dongliang Zhuang.

FDA Presentation - Dongliang Zhuang

DR. ZHUANG: Good morning. My name is Dongliang Zhuang. I'm the statistical reviewer for this NDA.

In my presentation today, I will cover study

sample size, subject disposition, demographic and baseline information, as well as the efficacy evaluation and the submission.

I'd like first to present study enrollment information. This information will form the basis of one discussion question that we will see later. Three studies were planned to enroll 160 subjects for each study population. However, none of the studies reached the enrollment goal.

Study 002 enrolled 147 subjects. Study 003 enrolled 130 subjects. Study 001 had a very low enrollment. It enrolled only 58 progressive keratoconus subjects and 49 corneal ectasia subjects.

According to the applicant, the low enrollment in this study was due to the early termination of the study after the investigator left the site.

Before I move on to discuss the subject disposition information and efficacy evaluation, I would like to remind you of some design features of these three trials.

In these trials, sham subjects had the option to receive CXL at month 3 or 6. For those subjects who received CXL, their subsequent study visits were reset and followed the same schedule as those subjects originally randomized to CXL. The study visits are displayed in the next two slides.

After the study eye received treatment on day zero, subjects in the CXL group and subjects in the sham group whose study eye did not receive CXL were followed for 12 months, and the efficacy outcome was evaluated at months 1, 3, 6 and 12, as shown in this diagram.

Sham subjects had the option to receive CXL at month 3 or later. This diagram shows an example in which a sham study eye received CXL at month 3, and it was followed for another 12 months according to the same visit schedule as the CXL group from day zero to 12 months.

The number of sham study eyes that received CXL by visit is shown in this table. Total, there are over 80 percent sham study eyes that received CXL at a different time visit in each study, mostly

at visit 3 and at month 6.

I will now discuss the subject disposition and the patient demographic information. For progressive keratoconus subjects, 69 percent of CXL subjects and sham subjects in study 001 completed the first 12 months of study. A 12 month completer is defined as CXL subjects who completed month 12 visit or a sham subject whose study duration is at least 12 months from day zero.

The overall completion rate for the study was low because the study was terminated early after the investigator left the site. The completion rate was 99 percent and 88 percent for CXL and sham arms in study 002.

For corneal ectasia subjects, 83 percent of CXL subjects and 68 percent of sham subjects in study 001 completed the first 12 months of the study. In study 003, the completion rate was 80 percent for both arms.

Of the progressive keratoconus subjects, about one-third were female. The majority of them were white. The mean age was between 30 and 37.

The average Kmax at baseline was around 60 diopters. And the best spectacle corrected visual acuity was around 33 liters.

Corneal ectasia subjects had a similar composition as the progressive keratoconus subjects in terms of gender and race. However, they were several years older, had a lower Kmax, but higher visual acuity reading at baseline.

The primary efficacy evaluation was based on the corneal curvature over time, as measured by maximum keratometry, Kmax, in the study eye at baseline, months 1, 3, 6 and 12.

The primary efficacy endpoint was originally defined in the protocol as a change in Kmax from baseline at month 3. However, this endpoint was changed to month 12 in the statistical analysis plan. A justification for this change was not provided in the SAP.

A justification was later provided in the clinical study reports. According to the applicant, the change was made based on literature review that suggests corneal stromal remodeling

associated with the healing response of the CXL requires 6 to 12 months to stabilize. Therefore, a later time point, such as month 12, is better suited for evaluating the long-term clinical benefits of CXL treatment.

There are two items to note here. The SAP was finalized after last study visit, and a portion of the study results was published before study completion.

This slide shows key dates for study planning, execution, analysis, and the reporting for all three trials. This information may be helpful when you discuss question number 2 later.

To highlight several things, the applicant acquired the product in May 2010, near the completion of study 001. The other two studies were completed in the first half of 2011. The SAP was finalized in late 2011 or early 2012, after the last subject completed the study. Prior to the finalization of the SAP, a portion of the 12-month study results was submitted for publication in March 2010.

A study was considered a success if a statistically significant difference was demonstrated in the mean change from baseline in Kmax between CXL and the sham group, and a clinically meaningful difference of at least 1 diopter was observed in the mean change from baseline in Kmax between the CXL and the sham groups.

The primary efficacy analysis used a two-sample t-test. The analyses were performed on all randomized treated subjects. Subjects were analyzed according to randomized treatment. Additional analyses were conducted by the applicant, including the analysis of covariance with the baseline as the covariates and a nonparametric analysis.

The applicant used the last observation carried forward approach to impute missing data. This includes missing data due to subject withdrawal or intermittent missed visits.

For sham subjects who received CXL at month 3 or month 6, the last Kmax measurement

recorded prior to CXL was carried forward in the analysis for the later time points.

The LOCF, the last observation carried forward approach is illustrated in this slide using three hypothetical examples. The first subject, 1001, withdrew from the study after month 1, and the last available Kmax was at month 1. The value at month 1 was carried forward to later time points, as shown in red.

The second subject, subject 1002, received CXL at month 3, and the last available Kmax prior to CXL was at month 3. This value was carried forward to month 6 and month 12.

The third subject, 1003, received CXL at month 6 and the Kmax at this visit was carried forward to month 12.

The next two slides summarize the number of subjects remaining on randomized treatment and with Kmax values. This summary result addressed the question of how much data was carried forward from early times into the efficacy analysis at month 12.

For progressive keratoconus subjects, the

majority of the CXL subjects remained in their randomized treatment group through month 12 and had a Kmax measurement. For example, in study 001, 20 CXL subjects had a Kmax value at month 12 and 9 CXL subjects had a missing Kmax value due to withdrawal from the study.

On the other hand, the number of sham subjects who stayed in their randomized treatment, and had the Kmax measurement dropped dramatically at month 6, and it was reduced to zero at month 12.

As a result, for the applicant's analysis at month 12, all the Kmax values at month 12 for sham subjects has to be imputed from the month 3 or month 6 visit.

In study 002, the majority of CXL subjects had a Kmax value at month 12. Four CXL subjects had missing data. However, only two sham subjects remained in the study and a Kmax value at month 12. And for the remaining 72 sham subjects, their Kmax data from month 3 or month 6 was used in the applicant's analysis at month 12.

As we see in this table, corneal ectasia

subjects had a similar pattern to that seen among the progressive keratoconus subjects. Prior to presenting the efficacy results, I will make some comments regarding the applicant's analysis at month 12.

Because almost all the subjects in the sham group received CXL treatment at month 3 or 6 or withdrew from study by month 12, as shown in the table below, the applicant's analysis at month 12 essentially compares a Kmax at month 12 in the CXL group to the Kmax at month 3 or 6 in the sham group.

The applicant stated that their analysis at month 12 was conservative. I wanted to point out that this analysis may not overestimate the CXL treatment effect at month 12 provided the following two assumptions are true for untreated progressive keratoconus or corneal ectasia subjects. The two assumptions are related to the natural history of the progressive keratoconus and corneal ectasia disease.

The first one is that on average, Kmax

remained stable, or does not improve. The second one is that the variability of Kmax will not increase over time. The applicant submitted literature to support the first assumption. However, a decrease in Kmax from baseline at month 1 was observed in the applicant's progressive keratoconus studies. You are going to see this one later.

Furthermore, the applicant did not provide data to support the second assumption. We would like to have your input on these two issues.

I will present in the next two slides the applicant's analysis of the mean change from baseline in Kmax.

For progressive keratoconus subjects, a statistically significant difference between the CXL and the sham group was not demonstrated at month 3. From month 3 to month 12, CXL subjects had further reduction in Kmax, indicating improvement in the corneal curvature, while at the same time the mean Kmax for sham subjects increased. As a result, the treatment comparison

at month 12 reached statistical significance. The results from applicant's additional analysis were consistent with these findings.

For corneal ectasia subjects, statistical significance was achieved for the treatment comparison at both month 3 and month 12. Despite the further reduction in Kmax for CXL subjects from month 3 to month 12, Kmax was relatively stable for sham subjects.

The mean change from baseline in Kmax over time for progressive keratoconus subjects is shown in this slide. The right line denotes the CXL group, the blue line denotes the sham group. As I mentioned earlier, sham subjects had a decrease in Kmax from baseline at month 1. We see almost identical results at month 6 and month 12 for sham subjects since almost all Kmax data came from month 3 or 6 as a result of sham subjects receiving CXL at months 3 or 6 earlier.

For corneal ectasia subjects, a decrease in Kmax from baseline at month 1 was not observed. Our observation made about month 12 for progressive

keratoconus subjects applies to corneal ectasia subjects.

We conducted an exploratory analysis to evaluate the treatment effects regardless of adherence to the randomized treatment. In this analysis, the last observed Kmax value was used for all subjects, including the sham subjects regardless of whether the study eye received CXL treatment at month 3 or 6. The last observation carried forward approach was used for missing data due to subject withdrawal or intermittent missed visits.

This illustrates the handling of Kmax data for the sham study eyes that received CXL in our exploratory analysis. The observed Kmax value after receiving CXL are in blue and imputed Kmax values are in red.

The first subject, subject 1002, received CXL at month 3 and continued the study for another 12 months according to the same schedule as the CXL treatment group from day zero to 12 months.

The new visit after receiving CXL at month 3

and at month 6 was mapped to month 6 and month 9 relative to day zero, but there is no visit that could be mapped to month 12 because the next visit would be at month 15. Therefore, Kmax at month 9 was carried forward to month 12 for this subject.

The second subject, subject 1003, received CXL at month 6. The new visit at month 6 can be mapped to month 12 relative to day zero, but this subject discontinued prior to month 12. So Kmax at the last visit was carried forward to month 12.

The last subject, 1004, received CXL at month 6 and stayed in the study. The Kmax at the new visit at month 6 became the Kmax at month 12 relative to day zero.

This slide presents our analysis results. The results for the CXL group are the same as those in the applicant's analysis at month 12. On the other hand, for the sham group, our analysis showed improvement in Kmax compared to applicant's analysis.

This should not be surprising because a majority of the sham subjects received CXL at

month 3 or 6. The results in the sham group reflect the CXL treatment effect at month 12 after sham subjects received CXL at month 3 or 6. Therefore, our analysis presents an estimate of treatment effect at month 12 according to the intent to treat principle.

I've shown in this table the treatment difference of 1.1 for study 001, 1.5 for study 002, for progressive keratoconus subjects, and for corneal ectasia the estimate was 1.8 and .4. They all trended favorably in support of CXL treatment effect.

To summarize, the progressive keratoconus study did not demonstrate a statistically significant treatment difference at month 3 according to the protocol-defined primary endpoint.

The change of the primary endpoint to month 12 in the SAP happened after publication of a portion of study results. Because there are almost no sham data at month 12, a direct comparison between CXL and sham groups cannot be made at month 12.

However, we do observe Kmax improvement at month 6 and month 12 in the CXL group, whereas no Kmax improvement was observed in month 3 and 6 in the sham group for both populations.

The applicant's analysis, as well as FDA's exploratory analysis results at month 12 showed a favorable trend in support of the CXL treatment effect.

The corneal ectasia study demonstrated a statistically significant treatment difference at month 3, according to the protocol-defined primary efficacy endpoint.

Now, I'll turn it over to Dr. Boyd to continue the discussion of safety.

FDA Presentation - William Boyd

DR. BOYD: Thank you. We've already discussed that pediatric patients above or equal to age 14 were eligible to be enrolled if they otherwise qualified, and this table has age in the left column and the distribution in the corneal cross-linking treatment group or sham group.

This next slide has a little more

descriptive information. There's a difference in the definition of a pediatric patient in the drug regulations and the device regulations. In the drug regulations, a pediatric patient is described as a subject birth to less than or equal to 16 years of age, whereas in the device regulations, the pediatric patient is birth to less than or equal to 21 years of age.

If we look at the center graph in studies 001 and 002, so these are keratoconus subjects, you can see the difference in the two age groups by regulation, 14 to 16 years of age and 14 to 21. These columns have the number of subjects who received primary corneal cross-linking treatment, the number of subjects who had sham, the number of subjects who had their sham eye treated after 3 months, and the number who had fellow eyes treated after 3 months. There was one corneal ectasia subject aged 21 years at the time he signed the protocol consent, and he turned 22 before treatment.

These are observed values, the efficacy

results for these pediatric age groups. If we look at the ages 14 to 16, you can see at month 3 it was minus 2.6 in the corneal cross-linking group, and by month 12 that was minus 2.1. If we look at the ages 14 through 21, at month 3, that was minus 1.3, and at month 12, that was minus 2.3.

The next two slides have already been presented. These are the common adverse events. This particular slide has the number of subjects with adverse events reported by greater than equal to 2 percent of subjects through month 3 pooled. So these are pooled for keratoconus and for corneal ectasia, and you see the corneal cross-linking and the control.

Again, this slide has also been presented previously. These are ocular adverse events greater than or equal to 5 percent in any corneal cross-linking eye at any time. And these are broken down by keratoconus in study 1 and ectasia in study 1, keratoconus in study 2 and corneal ectasia in study 3.

So, again, the most common adverse events

for either indication at greater than or equal to 10 percent are corneal epithelial defect, corneal opacity, corneal striae, eye pain, and punctate keratitis. Most of these events appear to represent sequelae following corneal epithelial debridement.

A discussion question that we'd like you to consider is a comment on certain study design elements. The planned enrollment and size of the studies was 160 patients, 80 per arm, as originally planned. The actual enrollment was less. For progressive keratoconus in studies 1 and 2, that was 102 actually enrolled in corneal cross-linking and 103 in sham. And in studies 001 and 003 for corneal ectasia, the actual enrollment for the cross-linking was 91 versus sham 88.

Another discussion question for later on is we'd like your discussion on any other potential safety issues.

Regarding corneal endothelial cell counts, and this has also been previously covered, I'm going to present the results for baseline and

months 3 and 12 from studies 001, 002 and 003. Months 1 and 6 were not planned visits for endothelial cell count determinations. And the p-values that you'll see in these tables shouldn't be used for statistical inference. They've not been adjusted for multiplicity.

So these were the observed values for keratoconus subjects in study 1. You can see at baseline in the corneal cross-linking group. The mean cell count was roughly 2700, and at month 12, again, roughly 2700.

For the corneal ectasia subjects in study 1, at baseline, the endothelial cell count in the cross-linking group was roughly 2400, and at month roughly 2300.

For study 002, which was the keratoconus study, the mean at baseline, 2600 for the corneal cross-linking group, and at month 12 roughly 2600.

For study 003, which was corneal ectasia, at baseline, the mean endothelial cell count for the cross-linking group was roughly 2500 and at month 12 roughly 2400.

Per the applicant, the variances observed in the endothelial cell count data sets for the studies represent inherent errors of measurement of the endothelial cell counts in the keratoconus and corneal ectasia populations, and the values were reconfirmed against the source documentation.

Another discussion question we'll come to later is we'd like you to discuss your interpretation of these endothelial cell count findings.

Intraocular pressure measurements were to be done at each treatment and follow-up visit. However, there were many protocol deviations. But a total of roughly 3,000 IOP measurements were performed over the course of the three studies. One patient was reported to have an IOP elevation at one visit, which was defined as an IOP greater than 30 millimeters of mercury. Subsequent measurements were within normal limits for that subject.

There were additional safety outcomes collected. The protocol included manifest

refraction, visual acuity, central pachymetry as secondary efficacy criteria. However, in the statistical analysis and clinical study reports, these endpoints were summarized as safety endpoints.

At this point, I'll turn it back over to my CDRH colleague, Maryam.

FDA Presentation - Maryam Mokhtarzadeh

DR. MOKHTARZADEH: As previously stated, CDRH has been consulted on this NDA to provide a device perspective. Based on the information presented in CDER's briefing material and the panel presentation thus far, the following slides will focus on additional topics we would like the panel to discuss.

Please refer to the presentation by FDA's statistical reviewer, Dr. Zhuang, for the study details discussed in this question. For both proposed indications, the studies were to evaluate efficacy 3 months after treatment, as reflected by the protocol-defined primary endpoint. For the progressive keratoconus population, statistical

significance was not achieved at month 3. Statistical significance was achieved at month 3 for the corneal ectasia population.

The statistical analysis plan submitted after the last patient visit extended the evaluation of efficacy to month 12, and the subsequent analysis used a last observation carried forward, or LOCF, strategy to impute missing data resulting from patient withdrawal, as well as to impute data for sham subjects receiving cross-linking treatment at month 3 or 6.

Please discuss the strengths and weaknesses of the trial design and analysis, including the effect of the following on your evaluation of product efficacy: the potential introduction of bias; number of subjects available; the use of LOCF; and, the stability of corneal response to treatment.

Please refer to Dr. Boyd's presentation on the pediatric population studied for the information pertinent to the following question regarding pediatric use.

In these studies, at the time of treatment, there were the following number of pediatric subjects enrolled, stratified by less than or equal to 21 years and less than or equal to 16 years, as previously discussed.

For the progressive keratoconus population less than or equal to 21 years of age, there were 19 subjects in the treatment arm to receive cross-linking and 14 subjects in the sham control arm. For the keratoconus population less than or equal to 16 years of age, there were 6 subjects randomized to receive cross-linking treatment and 4 subjects in the sham control arm. There were no pediatric subjects in the corneal ectasia population at the time of treatment.

For the proposed indication for progressive keratoconus, please discuss what is the minimum age supported by the data and the applicability of extrapolation from adult data.

This study undertook collection of a tremendous amount of data, as evidenced by the variety of assessments you have seen listed in the

study visit schedule, which was included both in the CDER's briefing materials and also in Dr. Boyd's presentation on slide 37.

A large number of assessments were performed at study visits in addition to those for which analyses were presented in CDER's briefing materials. The original protocol stated that a detailed statistical analysis plan will be developed for analysis of all data for this study.

However, as noted in Dr. Zhuang's statistical presentation on slide 49, the statistical analysis plan, or SAP, was not submitted until 2011 after the last subject completed the last study visit and after a portion of study results were published.

Data was collected according to the protocol. However the analyses were limited to those in the SAP submitted in 2011, which introduced changes to the endpoints and analyses pre-specified in the protocol.

In light of the information you have seen, please discuss your recommendations regarding the

need for analyses, if any, on the additional data that had been collected during the clinical trials to adequately characterize the safety and efficacy profile of this combination product.

Thank you.

Clarifying Questions

DR. AWDEH: Okay. Thank you for that. We will now move on to clarifying questions for the FDA. Dr. Belin?

DR. BELIN: On using the last observed carried forward, was that used both on the efficacy and on the safety parameters, and was it also used both on sham and treatment?

DR. ZHUANG: For efficacy, yes, for both arms, but no imputation for safety.

DR. BELIN: So it was not used for safety.

DR. ZHUANG: No.

DR. BELIN: Okay. Thank you.

DR. AWDEH: Dr. Weiss?

DR. WEISS: In terms of assessing whether that's a right way to look at things, you did mention it would depend on the variability of the

Kmax and the variability of the refraction.

Do we have any information in individual subjects what we could expect the variability of either of those to be in this study?

DR. CHAMBERS: This is Wiley Chambers. We have the actual data going through. We don't have any analyses that look at any other trends. I'm not sure how else -- I mean, if there is a particular way that you think the data should be looked at, we would be interested in knowing that and we'll ultimately provide that kind of analysis.

DR. WEISS: And a follow-up or a second question is in terms of looking at the pediatric age group. On slide 70, there is an effect at month 3, which goes down at month 6, which goes up at month 12 in age 14 to 16 and age 14 to 21. From my recollection, that wasn't seen in the adults.

Statistically, when the trend is looked at in adults versus pediatric, does it look like this is a different population from the way these results are or statistically would you say that you cannot reach any assessment on that because of the

actual number of subjects?

DR. CHAMBERS: This is Wiley Chambers. So if you take a look at the numbers that are involved in the pediatric patients, it's a very small number. And I think that the differences that you're seeing reflect the small numbers.

DR. AWDEH: Dr. Huang?

DR. HUANG: This question is directed toward Dr. Zhuang. On slide 64, this is for my clarification. There are three studies at two months by your exploratory analysis. Your data seem to indicate at 12 months, for the corneal ectasia group, the treatment is not effective or there's no significant difference. Is that correct? The last line of slide 64. It's on page 32.

DR. ZHUANG: So you're looking at the corneal ectasia subjects only, right?

DR. HUANG: Yes. The last line, UVX-003.

DR. ZHUANG: But there's a reduction of .5 for the CXL group and also a .2 reduction in the sham group. As I discussed in the presentation,

the sham subjects -- for the sham subjects, we include all the data of the CXL. So actually that includes the treatment effect at month 12 after the sham study eyes cross over to CXL at month 3 or 6.

DR. HUANG: This is Andrew Huang. Does that mean that the data by your exploratory analysis does not support the efficacy?

DR. ZHUANG: We are looking at the trend. The trend is in favor of the CXL.

DR. AWDEH: Dr. Belin?

DR. BELIN: I don't have the slide number. It's on page 35. It's the one that shows the pediatrics primary sham, sham eye treated, and fellow -- slide 69.

Either I'm reading it wrong. How can you have 19 primary eyes treated and two more fellow eyes treated than primary eyes?

DR. CHAMBERS: This is Wiley Chambers. The fellow eyes could be treated either from the sham or from the --

DR. BELIN: So that's a combined number.

DR. CHAMBERS: That's correct.

DR. BELIN: Okay. So then the primary eyes that were treated were 8. Is that correct?

DR. CHAMBERS: I'm sorry. Where do you see -- there are 19 --

DR. BELIN: If the 21 is inclusive, it includes the 13 on column 3, which is sham eyes treated after 3 months. That leaves 8 eyes.

DR. CHAMBERS: No. So fellow eyes are separate. You have treatment eyes and sham eyes. Each of them have a fellow eye.

DR. BELIN: Correct. But we only have two eyes. So how can you have 21 fellow eyes if you only had 19 primaries?

DR. CHAMBERS: Because some of the sham eyes had fellow eyes. So there's a total of 33 that were eligible.

DR. BELIN: Okay. So the shams actually had both eyes. Okay.

DR. CHAMBERS: The sham could be treated later on, the fellow eye could get treated later on.

DR. AWDEH: Dr. MacRae?

DR. MacRAE: We have a number of corneal specialists here that understand this, but if you look at the pediatric keratoconus studies and the international data, these eyes are clearly more progressive in terms of the progression of the cone.

So it's not surprising that the sham eyes would -- the individuals that were sham eyes would be more likely to be treated eventually. The assumption here is that they progress more rapidly. And in the studies that have been done by Rabinowitz and others on pediatric graphs here in the United States as part of clinical trials, they find that they are much more aggressive. And if you read their literature, basically, they're recommending treating these -- some of the literature at least says anyone under 24 that probably should be treated even if there is no sign of progression.

So there clearly is concern that these eyes are much more aggressive in terms of their disease, and I suspect that that's why the sham eyes tended

to be treated more aggressively basically.

DR. AWDEH: Dr. Weiss?

DR. WEISS: Were adverse events broken out for the pediatric age group? In terms of adverse events that were reported, do we know how it looked -- how many of those were pediatric?

DR. CHAMBERS: This is Wiley Chambers. The information was broken out to us, but we don't -- the information was all reported by individual patient. We do not have it broken out by pediatric patients. I don't know if the applicant does or not.

DR. WEISS: I would suggest that that would be helpful to obtain, if at all possible, during the meeting if we're going to be looking at the pediatric group separately.

DR. HERSH: Peter Hersh. We'll try to get that information for you at the break.

DR. AWDEH: Dr. Feman?

DR. FEMAN: Perhaps someone could clarify the whole point about what is meant by a combination product? Does that mean that we all

have to be in agreement with all aspects of this, of both the machinery, as well as the drug agent, that you can't separate thinking from one product to another?

DR. AWDEH: Could you restate the question, please?

DR. FEMAN: My concern is that this is called a combination product. If you think the concept that they're bringing forward is good, does one have to say this is the only machine that can work with this particular medication or can one say that you can create a UV-A machine off of some stuff. I see your finger up, so she may have an answer.

DR. EYDELMAN: Dr. Eydelman, CDRH. Yes. You are correct. As a combination product, those components have to be proven to be safe and efficacious for the product to be approved.

DR. AWDEH: Are there any other questions? Michael Pfleger?

MR. PFLEGER: A quick one for Maryam. Maybe you can tell us. One of the questions you asked

was do we see any concern about the device that they're proposing. So the sponsor had said that they had done a lot of studies that demonstrate that it produces the same energy and exposure.

So is the agency satisfied with that portion? So if the box is a different shape or things like that, that's obviously not much of a concern. But are you satisfied with the piece of the device that's important?

DR. EYDELMAN: This is Dr. Eydelman again. I'll take your question. As Maryam presented, she was asking for the panel input on specific aspects of the device differences that were presented in the question and the similarities that were presented by the sponsor.

MR. PFLEGER: If I can, that doesn't address the question I have, because one of the questions that the panel is being asked to address is if they are comfortable with the device. And the size of the box that it's in obviously is not especially relevant for a discussion of is the device producing the same UV-A exposure.

So it's less of a concern, obviously, that if you say that it produces the same levels of UV-A exposure, then that answers I think a portion of the question.

So has that portion been studied, and do you have a determination on that?

DR. EYDELMAN: The device evaluation is being currently conducted. The aspects of the device differences that we're seeking panel input are clearly summarized in our question. However, if the panel wants to provide input on other aspects, we're here to listen.

DR. MacRAE: Scott MacRae. So I asked our physicist to take a look at this information, and basically they feel that it's not -- at the University of Rochester -- and they don't feel that this is -- they feel that these are equivalent devices basically, as long as it meets the criteria that the agency is looking at.

So delivering that energy level at the cornea, whether you're using one technique or one device versus another, they didn't feel that it was

significant.

DR. AWDEH: Let's try to keep focused on the data that we have in front of us for the purpose of the meeting. Sorry, go ahead.

DR. EYDELMAN: If I can just add, I guess I'm not sure what information Dr. MacRae was sharing with people who aren't around this room, but we're asking that the information be done based on the information that's being presented by the FDA to the panel.

DR. MacRAE: Just to clarify, I just asked them about comparing the Avedro device to the other device, and do they feel that it's equivalent. So I wasn't giving information out from this system.

DR. AWDEH: Are there any other clarifying questions for the FDA? Dr. Weiss?

DR. WEISS: I could use some input from the FDA as to the importance of the zone. Are there studies that show that if you use one zone size or a smaller size versus a larger size, you'll have a difference in effect, because we're asked to be looking at nine versus the various zones that were

suggested and I don't really know how to interpret that.

DR. MOKHTARZADEH: This is Maryam Mokhtarzadeh. I think that's an excellent question. You're asking what the significance is of the illumination beam diameter on the treatment effect.

In the literature that I read and the discussion that I gave with regard to how investigators were advised to choose the diameter, the discussion focuses -- discussions that I've read have focused on safety considerations. For example, the intent to center the beam, minimize exposure to the limbal stem cells. However, I think it's a very good question what the impact on effectiveness is.

I have not seen a definitive study to that effect. However, I welcome the sponsor to provide additional information if they're aware of literature or any other information that specifically addresses that question.

But like I said, the discussions I've read

tend to focus on the safety.

DR. AWDEH: So I have a follow-up question, and the sponsor can answer this if they'd like.

Knowing that and that you knew the treatment zones in the original trial, what was the rationale for selecting a treatment zone of 9.0 for the new device?

DR. MULLER: David Muller. The question may be better answered if I had a couple of slides, but I may be able to address it later. But I think just to get started, as you note, we have a very fine alignment device. And certainly, one of the concerns, as you've heard addressed, was to protect the limbal stem cells, not to be near those.

If you look at the normal cornea, if you took 9 millimeters, and recognizing that the disease we're dealing with is always on the inferior side, we were sort of shading it a couple hundred microns, feeling that 9 millimeters covered the area of disease.

The device is provided with a thumb adjustment so that during the course of the

procedure, patients are always moving. So it allows with very high precision to keep the beam centered on the eye and just a little, a couple hundred microns less concern over worrying about safety issues.

There wasn't any specific reason other than we felt that 9 millimeters covered the range.

DR. AWDEH: Okay. Thank you.

DR. MacRAE: Question? We can ask it later.

DR. AWDEH: Go ahead. Sorry.

DR. MacRAE: I'm just curious. Had there been studies on limbal stem cells with this device? Maybe we should talk about that later. With the current device that you're proposing.

DR. HERSH: We did not do specific studies regarding limbal stem cells. There were no AEs or SAEs reported regarding any problem with them afterwards, though.

DR. LEGUIRE: Larry Leguire. There is really no data about patient satisfaction here, although I think -- and this is for the experts present and FDA -- if literally every patient in

the study, the vast majority of them have crossed over, I would think, and this is just an opinion, is if the treatment was found to be effective, well tolerated, basically say that patients would have a tendency to cross over. And if they found the benefits not worth the risks, that they simply would not have crossed over.

So my question is can I use the crossover data for patient satisfaction?

DR. CHAMBERS: This is Wiley Chambers. There was a patient questionnaire, as was described. There was not an analysis done that was presented to us. So I can't comment on any analysis of the patient survey.

As far as the crossover as a judgment, could you be more specific of how you would view that as an interpretation of patient satisfaction?

DR. LEGUIRE: Sure. Larry Leguire. If I'm a patient in a study and had one eye done, and it's an option for me to have the other eye done, well, that decision would be based on how I did with the first eye treated. And so if I'm not happy with

the first eye treated, I'm not going to have the second eye treated. That's just how it works. And over the years, 40 years of doing eye research, that's what I find subjects to do.

If something is well tolerated, if they benefit from it, do it again on this other eye. But if they had reservations, wait a minute, I don't see much change, this hurt, I didn't like it, there would be more dropout and less likely to do the other eye. That is my reasoning.

DR. CHAMBERS: This is Wiley Chambers. So we did not do any analysis that incorporated what you're asking.

DR. EYDELMAN: Yes. We believe, however, that the patients' voices are important and the agency is committed to eliciting patients' input on many aspects of product development and evaluations.

We're also committed to evaluation of patient-reported outcomes, when relevant, and in the medical product evaluation process, as evidenced by our patient-reported guidance

document. Therefore, we request the committee's recommendations regarding additional analysis on such data collected.

DR. AWDEH: Thank you. I have one question for the FDA. There were four patients that the sponsor had mentioned in their presentation that had greater than a 15-letter loss in best corrected visual acuity, 1 in the keratoconus group and 3 in the ectasia group.

Is there anymore data on those four patients you can share with us? Specifically, are these patients that had an improvement in Kmax or not, or a corneal scar or some other thing that happened in the event of treatment?

DR. BOYD: As I recall, it was unrelated to the Kmax. I don't have specific features that would isolate those four patients. The applicant may, but I don't recall that we had that.

DR. AWDEH: Does anyone on the sponsor want to respond to that question? Peter?

DR. HERSH: Peter Hersh. We looked into those four patients, and there were no preoperative

indicators or postoperative signs that accounted for them; age, there were no scars, there was no adverse event, there was no haze, there was no infection. There was nothing really that you could point your finger to as to why their vision was down with spectacle corrected.

They were not the same patients who continued ostensibly to progress either. So whether they're outliers or just that was their vision on that day, we couldn't really find any specific reason why their vision would be down.

DR. AWDEH: If there are no more clarifying questions for the FDA, let's use the balance of this time to go back to the sponsor. There were a few items from the morning session that you were going to come back to clarify for the group.

MS. NELSON: Hi. Pamela Nelson, regulatory affairs for Avedro. We are looking into the committee's questions. We appreciate the questions, and we'll be prepared to present additional information after the lunch break to clarify. Thank you.

DR. AWDEH: Okay.

DR. MacRAE: I have another question for the sponsor. In the one-week epithelial defect data, 22 percent in the keratoconus group and 24 -- or 26 percent had epithelial defects that lasted more than a week. Can you comment on that?

DR. HERSH: Yes. Peter Hersh.

DR. MacRAE: It seems so large. It just seems like a large number.

DR. HERSH: Yes. The protocol had study visits a day, a week, and a week typically would be at the 5-day mark in order to remove the bandage, contact lens. And their next protocol visit was one month later.

So any patient who had any residual epithelial defect at 5 days when the contact lens was taken off would have an unscheduled visit to make sure they healed. So these 20-some-odd percent, which we can see here --

DR. MacRAE: Page 39 on CC-70.

DR. HERSH: Right, 22 percent in the KC group and 26 percent in the ectasia group

represented patients who were not completely healed at the protocol one-week visit and who would then come in afterwards to make sure that their epithelium was healed.

DR. MacRAE: Do we know how long it took, or what was the longest period that -- you can't give us all the details, but how long did it take? How many days after routinely did they bring those patients back for reevaluation, or was it just everybody did it according to their own different plan?

DR. HERSH: Typically, people would schedule an unscheduled protocol visit. There was not any protocol advisement regarding that. So typically, I know in our center, we would have them back in a couple of days or so to make sure that the epithelial had healed.

DR. MacRAE: Do we know how many had epithelial defects past two weeks?

DR. HERSH: I don't know offhand. We can try to check that in the database and bring that back to you if we do have it.

DR. MacRAE: Thanks.

DR. AWDEH: Okay. If there are no more questions for the agency, let's now take a break for lunch. We'll reconvene in this room one hour from now, at which time we'll begin the open public hearing session.

Please take any personal belongings that you may want with you at this time. Panel members, please remember that there should be no discussion of the meeting topic during lunch amongst yourselves or with any member of the audience.

Thank you.

(Whereupon, at 11:42 a.m., a luncheon recess was taken.)

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

(12:46 p.m.)

DR. AWDEH: I'd like to go ahead and start the afternoon portion of the session. To start, on the FDA side, I have one clarification, so I'll ask Dr. Zhuang to speak with his clarification.

DR. ZHUANG: This is Dongliang Zhuang. If you have your slides back, if you could go to page 32 and slide 64. So a question was raised about why the p-value in the FDA exploratory analyses are not statistically significant or not less than .05, in the analysis.

To answer the question, I would like to point out that the majority of the sham subjects received CXL at months 3 or 6. And their last observed Kmax value after receiving CXL was used in our exploratory analysis. As a result, our analysis results are conservative compared to the applicant's results in terms of having larger p-values and a smaller treatment difference compared to applicant's analysis. Therefore, we don't expect the p-values in our analysis to be

less than .05.

DR. AWDEH: As we're a little bit ahead of schedule, I'd like to give the sponsor an opportunity now to answer some of the questions that were posed this morning. So we have about 10 minutes for that. David?

DR. MULLER: David Muller. I'll start to answer a couple of questions. Dr. Weiss, you had questions about something in the literature regarding long-term follow-up.

We were able to find two articles, one, Tomita JCRS 2014, and it was a study with 30 eyes of accelerated cross-linking, 18 eyes using traditional cross-linking protocol, from baseline over 12 months showed a decrease of about .7 diopters, plus or minus .67 diopters. And that was over 12 months.

Then a second study, JRS 2014, page 843, and this was 44 eyes in 38 pediatric patients, average age 15.3 plus or minus 2. And those patients were followed for 2 years, baseline 57.1. At 12 months, they were 56K and at 24 months 56.1. So followed

over 2 years.

DR. WEISS: For the second study, which is of -- this is Jayne Weiss. For the second study, which is the most interest to me because it has a two-year follow-up, which is the longest follow-up, and it has the pediatric age group, the Kmax initially was 50 --

DR. MULLER: 57.1.

DR. WEISS: And then the final Kmax was?

DR. MULLER: 56.1 at 24 months.

DR. WEISS: And this was the 9 millimeter zone?

DR. MULLER: This was the 9 millimeter zone. Yes.

DR. WEISS: So the difference was the concentration of the riboflavin? What is --

DR. MULLER: The difference was the exposure time. So in these studies, you could get 5.4 joules in 3 minutes instead of 30 minutes. So it was the same energy dose, which the energy is -- and actually, this was 7.2 joules with slightly more energy. So the energy, when

considering cross-linking, the energy is really the dose. Riboflavin's the intermediate. So these had a 9 millimeter zone with slightly more energy delivered over 4 minutes instead of 30 minutes.

DR. WEISS: And adverse events on this?

DR. MULLER: Complications were -- there were no other complications other than pain reported the first 3 to 4 days during epi re-healing.

DR. WEISS: Thank you.

DR. MULLER: And, Dr. Huang, my colleagues have told me I might have misinterpreted your question. So I may have two different answers for it. I think if the question was related to absolute riboflavin intake, a typical daily dose for riboflavin for a normal person could be in the order of 30 up 30 300 milligrams. And the amount of dose contained in a full vial of riboflavin is about 2.6 milligrams. So it's well below that number.

Secondarily, if you had a question regarding riboflavin concentration on the endothelium, we

also performed a very in-depth controlled GLP study looking at the effect of riboflavin on the endothelium, and found that it concentrates up to about 0.5 percent, is where we stopped. We saw no effect on the endothelium. So if there was a build up in the aqueous, we wouldn't expect a problem from that either.

Did that help your question or did I get that closer?

DR. HUANG: Thank you.

DR. MULLER: Thank you.

DR. WEISS: Could you give me the name of the -- just the reference for the last article? Who were authors and when was it published?

DR. MULLER: Sure. The last article was JRS 2014, page 843. And it was a series of Turkish authors, whose names I won't be able to pronounce for you.

DR. WEISS: Can you spell them and not pronounce them?

DR. MULLER: JRS 2014, 843.

DR. WEISS: I mean, I actually would like to

look it up on PubMed myself because to me that has a tremendous amount of information that we're being asked to judge about your study but is not provided in your study; namely the pediatric age group in the 9 millimeter.

So if you have the first author with the initial, I'll look it up myself.

DR. MULLER: Sure. We can find that for you, but --

DR. WEISS: Okay. That's fine.

DR. MULLER: -- I would emphasize that the treatment parameters, except for 9 millimeters, are completely different than what's in this study. It's 7.2 joules at 30 milliwatts. So it's not an apples to apples comparison. I'm happy to provide you the data, though.

DR. WEISS: Thank you.

DR. HERSH: Peter Hersh to answer Dr. Weiss' question regarding the AE stratified to the pediatric age group. Here in a subset of patients from 14 to 18 years old, there are 7 patients that were observed. You can see here at 3 months that

three had the typical corneal haze, and one patient with these other AEs. At 12 months, there was only one AE, and that was glare in one patient.

If we now look at the age range 18 to 21, there were 12 patients that were observed at 3 months. Nine of them had, again, the typical corneal haze, and then there were 3 and 2 and 1 of these various other AEs. When we looked at 1 year, there was only 1 AE of reduced visual acuity out of the 12 patients in this age group.

To answer Dr. MacRae's question regarding persistence of epithelial defect, unfortunately we don't have the information with us to analyze, but I do know from my own experience and from a number of patients, typically I would see these patients back two days later in the vast majority or were healed at that point. There were no -- as I know, there were no persistent epithelial defects as we would think of them.

DR. AWDEH: Dr. Eydelman?

DR. EYDELMAN: I just wanted to provide clarification in light of Dr. Weiss' question to

the sponsor. Different device setting with respect to the parameters discussed were qualified as a different device from CDRH perspective.

So I guess the question you originally asked if there was any data available with the product proposed for marketing, I guess I heard no? I'm not sure if I heard the answer, so that's why I wanted the clarification.

DR. MULLER: David Muller. The reports that -- the studies that I described were not studies done at 3 milliwatts.

DR. AWDEH: Dr. Weiss?

DR. WEISS: Jayne Weiss. Seventy-five thousand patients treated, and no one's written an article that's accepted?

DR. MULLER: These patients -- I'm sure there are more articles that are in publication, and we could provide you more. But again, none of them were done with the parameters that we're seeking approval for here.

DR. WEISS: Jayne Weiss again. So how do we approve this and say it's substantially equivalent

if there's no data that it's ever been -- that you can provide us or anyone has published?

DR. MULLER: Well, in response -- in our filing with FDA, we had to show the equivalence of the device with respect to its performance. They're really only two criteria which are really power delivered and that time that that power is delivered over.

The issue with the spot size between 9.5 and 9 millimeters, you have to recognize this is a 250 micron difference on the inferior part of the cornea. With 9 millimeters, we actually cover the cornea totally to where any disease would be.

So it is virtually equivalent to the clinical trial device. And in fact -- if I could have the slide that shows the beam focused -- the one that shows the working distance.

So if you look at the way the beam is applied to the eye, it first passes through a focus, and then it spreads out. And it's designed to have what's called basically a confocal region, a region over which the beam is uniform. So if you

look at the difference between the UVX system and the KXL system, you'll see that the UVX system is what's known as a faster system.

So what happens, when the patients are being treated, as they're lying there on the bed breathing, moving, and the like, the movement over 250 microns is happening on a regular basis. The slower system that we have that provides the beam that comes down the way it does, there actually is less variability on the patient.

So the patient's actually getting -- with our ability to align the system and both X, Y and Z, the patient's getting it more uniform in a more even distribution as opposed to a system in which there could be substantial vertical movements.

Peter, you may want to comment on this.

DR. HERSH: I use both of these systems in different clinical trials. As presented, the important aspects of the system are identical. You're getting the same ultraviolet power, the same interaction with the riboflavin.

So the cross-linking procedure that we're

doing is the same. The newer system is much more patient friendly and much more surgeon friendly. With the original UVX system, one would literally have to hold the patient's head and talk to the patient throughout 30 minutes, look here, look there, and centration was difficult. Z-axis centration was difficult as well. We would literally have to go and stand there with a ruler, and every five minutes check it with a ruler.

Here, as with other equipment we're used to using, we can get an accurate Z-axis. We can get an accurate XY-axis, easy to keep centration appropriate.

In the original system, there's a lot of movements, very difficult to keep that beam centered within the central cornea with any really good degree of moment-to-moment accuracy. You keep the light in the proper position to have the proper treatment, but if one looks at an actual treatment, looking at UVX and the current system, the current system allows accurate and very controlled accuracy in the center of the cornea and at the Z-plane.

Therefore, I think it's also a safer procedure if one has any concern about limbal epithelium because you can keep this within the center cornea without the drifts that we had seen with the UVX system. And physicists, engineers have all showed the equivalency of the two systems from the actual working end of it.

The cross-linking that it's doing, it's doing it the same way. It's doing it with a standard protocol, the Dresden protocol. That's been used all over the world for all these years, and that is the one tried and true, so to speak, accepted, published protocol where we really know what results we're getting.

So I think from a clinician's point of view, this is certainly the unit we would want to use.

DR. AWDEH: Thank you. I have two follow-up questions for the sponsor before I move on. Dr. Brown?

DR. BROWN: Regarding the epithelial defects, were there any specific medications, drops, anything that was recommended in the

protocol? I don't see it in the protocol or the labeling during that period while the epithelium is healing.

DR. HERSH: Yes. The investigators were instructed to use an antibiotic and corticosteroid 4 times a day for 1 week, at which point the antibiotic was discontinued, and the corticosteroid was continued for one more week. A bandage contact lens was placed in all patients.

Recommendation was to remove it at day 4 or day 5. And that actually gets to the question of some of the more persistence because if patients would come in at the early end of the window and have their lenses taken out, then the next visit would technically be an AE because if they came in on day 6 after coming in on day 4, they would be listed as having persistent epithelial defect.

So contact lenses were placed on everybody, and the investigator could use a nonsteroidal and non-preserved artificial tears as was her usual postoperative regimen.

DR. BROWN: Thank you. And then just one

other issue. Regarding the requirement for the corneal thickness to be 400 microns, is that based on the safety issues with the endothelium, or is there also an efficacy issue in terms of that specific thickness?

DR. HERSH: The 400 level is a number that comes from the early laboratory research out of Dresden. As the UV beam enters the cornea, it's attenuated, so the power diminishes at each level. And 400 microns at the time was felt to be a very safe level for the endothelial cells.

So in the Dresden protocol, it has always been to either have 300 microns or to swell to 400 microns before starting. So many of the -- a lot of the published literature that has been cited out of Australia, out of Europe, uses that same technique.

DR. BROWN: And what would be the safety margin in terms of -- if a clinician were to do it too early in patient whatever at 350 or 380, do you have a feeling what the safety margin is?

DR. HERSH: Well, it is a big margin of

safety because it turns out, as we learn more about cross-linking, about riboflavin chemistry and exactly what's being done with activator and cingulate oxygen, that there is indeed a greater safety level than the 400 that we're working with here.

I know that the in vitro group has a lot of data published regarding some of those safety levels and the attenuation of the energy as it goes through the cornea.

DR. BROWN: Maybe it would be 10 percent or 20 percent of a safety margin?

DR. HERSH: I would say there's at least 20-25 percent safety margin.

DR. AWDEH: The final question is from Dr. MacRae.

DR. MacRAE: I just have a question. Are we -- is it okay to look at outside literature? Because there are a number of pediatric studies and clinical trials that essentially use the Dresden protocol. Is that acceptable or are we going to confine ourselves to purely this data? Because

there's a lot of other information that --

DR. AWDEH: For the purposes of today, we're looking at the data that was presented to this panel to review before the meeting and to discuss today.

DR. MacRAE: Okay. Thank you.

Open Public Hearing

DR. AWDEH: Let's move forward to the next portion of our day.

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 hearing session of the advisory committee meeting, the FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its products and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial interest and relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issue before them.

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

Thank you for your cooperation.

That said, will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record. And speaker number 1 is David Glasser.

DR. GLASSER: All right. Thank you. My name is David Glasser. I'm speaking on behalf of The Cornea Society. I want to thank the panel for the opportunity for the society to present its opinion in support of collagen cross-linking.

I have no financial interest in the manufacturer, the process, neither does The Cornea Society. I've received no reimbursement for travel or time off or anything else. I'm just here to express our support.

The Cornea Society is an academic medical organization representing over 800 corneal surgeons. Corneal surgeons provide medical and surgical care to patients with keratoconus. We're the physicians that take of the tough cases.

As you all know, cross-linking is the

application of riboflavin and UVA to create new chemical bonds, increasing corneal rigidity. The most frequent indication is keratoconus. Other indications include ectasia after refractive surgery, which is being considered in this application, and some physicians also use it for infectious keratitis.

You've all seen the data. You've all had a chance to look at the peer-reviewed literature. I'm not going to review any of it, except to say that there are hundreds of articles out there. And in the society's opinion, the literature clearly indicates that cross-linking halts the progression of corneal steepening and improves steepening a little bit.

The risk of complications we believe is low, and we believe that the existent literature supports the concept that cross-linking, if applied early enough in the course of the disease, will reduce the need for corneal transplantation or other invasive surgery which has much higher risks and costs than cross-linking itself.

We also believe that cross-linking will improve and extend contact lens tolerance, allowing patients to avoid either the need for rigid gas-permeable contact lenses, or very expensive specialty contact lenses that can cost $700 and more per lens.

The disease burden is substantial. First, I must apologize for a typo here. I was reading off the wrong line of a spreadsheet. The actual number of corneal transplants done in the United States for corneal ectasia and thinning in 2013 was 6,894 according to the Eye Bank Association of America, 2013 statistics.

That's a significant number of patients who had corneal transplantation for keratoconus. Had those patients been able to access cross-linking at an early course in their disease, a substantial number of them would have been able to avoid that surgery.

In addition, the prevalence of keratoconus in the general population in the U.S. is subject to a wide variance depending upon which study you

read, varying by a factor of about 10, but suggesting that there are somewhere between 190,000 to over 2 million people in the U.S. with keratoconus.

These are old studies and were done before the advent of current diagnostic technology. So the current numbers are probably much higher than that. So there are a significant number of people who would stand to benefit from cross-linking. As it currently stands, without an approved device, there's inadequate access to safe cross-linking care.

Despite limited registered clinical trials, there are a lot of people who have to go to overseas referrals or who have to use unapproved equipment by physicians in the United States who are using this equipment because they believe the procedure is beneficial.

To summarize, the Society's position is that we support collagen cross-linking as a safe and efficacious tool which can halt the progression of keratoconus and ectasia before it advances to the

point of requiring more expensive contact lenses or more invasive corneal transplantation surgery. Thank you.

DR. AWDEH: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and organization you're representing into the record.

DR. DAYHOFF-BRANNIGAN: Hi, my name is Margaret Dayhoff-Brannigan, and I am a senior fellow at the National Center for Health Research. Our research center scrutinizes scientific and medical data and provides objective health information to patient providers and policymakers.

We do not accept funding from device companies and therefore have no conflicts of interest. Thank you for the opportunity to speak here today.

I completed my Ph.D. in biochemistry and molecular biologically at the Johns Hopkins School of Public Health. Prior to receiving my doctorate, I conducted research at the Wilmer Eye Institute at Johns Hopkins. I bring a perspective as both a

researcher and an advocate for improved safety of medical devices here today.

It's clear that patients suffering from keratoconus or corneal ectasia need treatment options. The risk benefit analysis may support approval of cross-linking for these patients. However, we are very concerned about the data presented here showing limited efficacy.

More than 25 percent of patients treated show k-max values that did not improve or stabilize. We are also extremely concerned about the potential for off-label use of this technology. The incidence of adverse events from the cross-linking procedure is very high. So this procedure should not be used, except for in these diseases and conditions.

We are already seeing LASIK procedures that include cross-linking in Europe, where standards are much lower than in the U.S. This puts patients at unnecessary risk. Approving cross-linking could be a slippery slope that we need to avoid in our country to keep patients safe.

If cross-linking is approved, there are a few ways to prevent or at least greatly reduce off-label use. Firstly, a black box warning that specifies the benefits are not proven to outweigh the risks for LASIK patients, and the device is only approved for progressive keratoconus or corneal ectasia.

The black box should explain the risk of decreased vision, eye pain, irritation, infection, and severe chronic dry eyes. It should also explain that at least 25 percent of patients have no improvement after treatment.

Second, FDA approval should be limited to patients over 16. Adolescence is a time of rapid eye development, and it's inappropriate to extrapolate the results from adults to adolescents.

Third, we urge the committee to recommend that FDA strictly limit the marketing of cross-linking procedure to its approved purposes, progressive keratoconus and corneal ectasia on patients over 16.

The FDA has the authority to provide a black

box warning about off-label use. I urge you to ask the FDA this question. Can FDA limit and enforce advertising, including in-office marketing? In addition, we strongly recommend two other safeguards.

First, FDA should require data on the off-label use of this device. Second, FDA should require the company to immediately start a post-approval study to determine the long-term effect of this specific device, particularly on teens and young adults.

The data presented by Avedro cannot confirm if the procedure merely delays the progression of the disease or if it's a permanent solution, and they show no safety and efficacy data from this newer device. If the procedure is not a permanent solution, then it is important that patients use that information in determining if the risk of adverse events is worth the delayed progression.

In conclusion, it's crucial that patients have safe and effective treatment options for progressive keratoconus and corneal ectasia. But

the evidence indicates this treatment would do more harm than good for LASIK patients.

To protect the patients who would benefit and those who are likely to be harmed, the FDA needs to use a black box warning and minimize off-label use of the product. Post-market approval studies will also provide valuable information about the risk benefit for undergoing the procedure. Thank you very much for your time.

DR. AWDEH: Thank you. Will speaker number 3 step up to the podium and introduce yourself?

MS. WARREN: Good afternoon. My name is Catherine Warren. I'm the executive director of The National Keratoconus Foundation. The foundation was started in 1986, and since then our mission has been to give information and support services to those who have keratoconus.

The textbooks say that keratoconus is first diagnosed in the teens, but we are finding that our doctors have the technology and the ability to diagnose patients with early keratoconus before

vision is actually affected, much earlier. We're hearing stories of 10 and 12 year olds with keratoconus who would benefit from this treatment if it were available to them at this younger age.

Parents call us constantly or patients call us constantly, depending on who they're talking to. A parent who finds out that their 10, 12, or 15-year-old has keratoconus is desperate to find out how to stop their vision loss and what to do about it. We offer them the information that we have, but up until corneal cross-linking became available, the only treatments available were contact lenses to correct their vision or eventually a corneal transplant surgery.

Contact lenses for keratoconus are extremely uncomfortable. They're difficult to fit. They require many changes over the course of sometimes a year. Sometimes patients need 2 or 3 different changes in their lenses over the course of a single year because of their rapid progression, and progression is much more rapid and aggressive in the younger child.

Once diagnosed, keratoconus affects their entire life, for their entire life. The blurring distortion, multiple images, ghosting, headaches, caused by keratoconus, impact every aspect of a keratoconic patient's eyes. Teens have difficulty in school, sports, social settings; so important at this age for their development.

As they get older and start to think about their future, they doubt they ability to be able to hold a job, pursue a career, go to college, or even develop a family and a relationship. Those who are interested and plan to enter the military, for various reasons, find that keratoconus disqualifies them from this service.

In mid-life they fear loss of employment because of lost time, going back and forth to doctors, constant contact lens changing, as well as their difficulty in applying for being able to do their jobs. Imagine the difficulty of wearing a lens for only 6 or 7 hours a day comfortably. What would do with the other hours of the day where you did not have any functional vision?

Another population that's grossly overlooked in the keratoconus population are the Down's Syndrome children or Down's Syndrome individuals who have a high incidence of keratoconus, cannot wear contact lenses, and are rarely offered the possibility of a corneal transplant.

They would be very well-served by having corneal cross-linking to preserve what vision they have. We have the ability to diagnose early. We have the ability to stop the progression of keratoconus or to at least halt the progression so that it slows to a much slower degree.

There's no cure for keratoconus, but there is corneal cross-linking, which offers a solution to the progressive vision loss, the years of painful contact lens wear and the fear of corneal transplant surgery, followed by more contact lens wear after their surgery.

These patients are anxiously awaiting approval of this procedure and I hope that this committee will grant approval for this vision-saving procedure, so that every patient in

the United States who is a candidate would benefit from this procedure. Thank you very much.

DR. AWDEH: Thank you. Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you're representing.

DR. SLADE: My name is Stephen Slade and I'm here today on behalf of AECOS, The American European Congress of Ophthalmic Surgery. First of all, thank you very much, Mr. Chairman, Richard, FDA, Avedro, and audience for the opportunity to share my thoughts.

I have no financial interest or relationship with Avedro and I paid my own way up here to talk today.

I'm a corneal specialist and I practice in Houston, Texas. I came today, up to this frozen world from Texas, because I believe strongly, as a corneal specialist, how much we need to have this technique, this procedure, corneal cross-linking for our patients.

I'm founder and past chair of AECOS. AECOS

is American and European members. Some of our American members have direct experience with corneal cross-linking through trials. Most of our European members have direct experience on a regular basis in their practices with their patients on corneal cross-linking.

Our society urges the panel to consider strongly the recommendation to FDA to approve this technique. Cross-linking, as discussed today, this technique works. There are papers now with 10-year follow-up. I could have brought slides, but I couldn't imagine a slide with data that hasn't already been shown.

It's, of course, a blinding eye disease, keratoconus. We're now able to halt its progression in the vast majority of cases with this patient -- tremendously patient-friendly technique, and we should take advantage of this.

It's a true fighting blindness technique. This is the reason that doctors such as myself go to medical school. This is the reason that ophthalmologists go into corneal, to practice, to

actually -- this is the pure science. This is fighting blindness.

When I finished my 10 years of training after university to become a corneal specialist, I planned to sort of make my living with two different diseases. I was going to do corneal grafts for people that had pseudophakic bullous keratopathy or complications from older intraocular lenses and cataract techniques, and keratoconus.

Thankfully, it's rare now to see a patient with a comprised cornea from an intraocular lens or from cataract surgery. Nothing could make me happier than to have a technique such as cross-linking for I can say that I have done my last graft on a keratoconus patient.

Again, AECOS and its members strongly urge the panel to recommend approval of this technique to the FDA. Thank you very much for your time and attention.

DR. AWDEH: Thank you. Will the next speaker, speaker number 5, step up to the podium and introduce yourself? Please state your name and

any organization that you're representing.

MS. COFER: My name is Paula Cofer. I am here as a private citizen and as an advocate for patients suffering from complications of refractive surgery. I paid my own way here today and I have no financial interest to report.

Keratoconus is not the same histopathological process as iatrogenic ectasia. My comments and recommendations pertain to the proposed indication for post-refractive surgery ectasia. Riboflavin UVA irradiation, smoking, diabetes, aging, all create corneal collagen cross-links.

Ectasia may present years after seemingly successful LASIK. Dr. Jorge Cazal asserted that at six months post-op, LASIK eyes experience a 48 percent reduction in corneal biomechanics. Permanent weakening of the cornea with a risk of ectasia is a primary reason that Dr. Morris Waxler petitioned the FDA in 2011 to withdraw approval of LASIK devices. Most cases of ectasia are never reported to the FDA and the true rate is unknown.

When LASIK was approved, the FDA established a minimum of 250 microns of cornea to remain untouched under the flap to safeguard against ectasia. The 250-micron guideline was not scientifically sound.

LASIK surgeons advising the FDA were more interested in maximizing the pool of candidates than in patients' best interest. David Muller, President and CEO of Avedro, was formerly chairman, CEO of Summit Technology, the company that brought one of the first excimer lasers to market in the U.S.

Since Muller's laser and competitor lasers were approved by the FDA, thousands, likely tens of thousands of LASIK patients have developed ectasia. LASIK surgeons deny that LASIK causes corneal ectasia. Stephen Slade, MD, quote: "I don't think refractive surgery causes keratoconus."

Daniel Durry, MD, quote: "We need to quit beating the legal fray on this that we've created some new disease, because the lawyers are having a field day by calling this a new disease, post-LASIK

ectasia, I question whether it really exists."

Dr. Durry was an investigator in the current study and in the PROWL Study which was part of the LASIK collaboration project. If he won't acknowledge LASIK complications, can the PROWL and Avedro data be trusted?

The MDR regulation requires reporting of serious adverse events. Currently, just over 100 cases of post-LASIK ectasia have been reported, consistent with gross under reporting for all complications of LASIK.

There were more patients with ectasia in the Avedro trial than the number that have been reported. Although they do not report ectasia cases as required, the industry maintains private databases of post-LASIK ectasia cases.

The Avedro brief for this NDA states, "Those with keratoconus have increased prevalence of anxiety disorders, poor mental health, difficulty performing social duties, and high dependency." It makes no mention of quality of life impact of iatrogenic ectasia.

The industry has repeatedly denied any link between a bad outcome from LASIK and poor quality of life, depression, and suicide. As a patient advocate, I am personally aware of 7 cases of suicide due to LASIK surgery. How many more are there?

Where is the real money to be made with cross-linking? LASIK Xtra uses cross-linking as a adjunctive standard LASIK prophylactically to stiffen the cornea following LASIK. Once the FDA approves the proposed indication for CXL, how long before LASIK surgeons begin performing LASIK Xtra off-label and on high candidates and how long before the FDA feels pressure to approve the LASIK Xtra indication, because that train has already left the station.

I ask the panel to recommend the following: 1) post-refractive surgery indication not be approved for cases without documented evidence of progression of the disease; 2) if CXL is approved, its labeling include a black box warning of potentially disabling eye injury; 3) CXL not to be

performed as a prophylactic simultaneously with primary LASIK, which would effectively pile additional risk and adverse effects onto an already harmful, unnecessary surgery.

In conclusion, in a televised debate with Dr. Morris Waxler, Dr. Stephen Slade said, "The patients that have had problems with older forms of LASIK are our focus, and we will do everything for them we possibly can."

Refractive surgeons should take ownership of the problems they create. I ask AAO and ASCRS to earmark foundation funds to assist injured patients for the burdensome cost of rehabilitation. Thank you.

DR. AWDEH: Thank you. Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any organization that you're representing, for the record.

DR. JOHN: I'm Dr. Thomas John. I have no financial interest. I'm currently in private practice in Oak Brook, Illinois, with an academic

appointment at Loyola University. As a member of the Corneal Clinical Committee of the American Society of Cataract and Refractive Surgery, ASCRS, I am here to speak on behalf of ASCRS, a medical specialty society representing over 10,000 ophthalmologists in the United States and abroad, who share a particular interest in cataract and refractive surgical care.

ASCRS strongly supports the approval of corneal collagen cross-linking for the treatment of ectatic corneal diseases. As most of you know, keratoconus is a bilateral, progressive, asymmetric, non-inflammatory corneal ectasia with an incidence of 1 in 2000 in the general population.

This disease affects mostly individuals during their second decade of life and often results in significant visual loss, devastating economic impact, and reduced quality of life. At the present time, because there is no cure or effective treatment for keratoconus and other similar ectatic corneal disorders in the U.S.,

these diseases continue to progress, especially during the early stages of life.

These patients typically experience gradual deterioration of their vision, which often requires frequent changes in their glasses and contact lens prescriptions. Many of these patients then move on to specialty contact lens fitting, which can become very difficult, frustrating and costly, as any eye care provider who encounters the scenario can attest.

With advanced stages of this disease many keratoconus patients eventually become contact lens intolerant and end up requiring full or near full thickness corneal transplant surgery. In fact, keratoconus is one of the leading indications, up to 20 percent of penetrating and deep anterior lamellar keratoplasty procedures performed in the U.S.

The first human study of cross-linking for the treatment of keratoconus appeared in the American Journal of Ophthalmology 12 years ago. Today, there are over 200 papers in the peer review

literature supporting the safety and efficacy of cross-linking for halting the progression of this ectatic corneal disease.

While cross-linking has become the standard of care around the world for these indications, this procedure is still not approved here in the U.S. Ophthalmologists in this country have been referring patients overseas for cross-linking for years.

Other practitioners have been offering the treatment as part of registered clinical trials. As of January 29, 2015, there are approximately 26 of these trials currently active. Some ophthalmologists in the U.S. are even offering cross-linking with unapproved UVA lights, lights imported from overseas, or lights approved for other indications, largely because they believe the risk of enforcement action is acceptable in order for them to offer their patient treatment for a condition that has no other FDA approved treatment in this country.

ASCRS believes the peer reviewed literature,

including uncontrolled observational trials and well-conducted prospective clinical trials, as well as the personal experience of many of our members, demonstrate the safety and efficacy of cross-linking.

We therefore, strongly urge the FDA to approve this application. Thank you.

DR. AWDEH: Thank you. Will speaker number 7 step up to the podium and introduce yourself? Please state your name and any organization that you're representing for the record.

MS. CHENAULT: Good afternoon. My name is Kathleen Chenault. I have no financial conflicts of interest regarding your proceeding today and have received no reimbursement of any kind. I'm here to tell you about my son.

Dillon is an 18-year-old high school senior. He chose not to be here today. He doesn't like dwelling on his vision problems and he doesn't like to be reminded of what remains ahead of him as a keratoconus patient.

It comes down to this. We must protect his future by preventing his vision from deteriorating further because of keratoconus. Dillon was diagnosed with the disease when he was 15. Our first question was what can we do? The answer was stark.

Here in the United States there's not much you can do; not compared with countries that have successfully pursued treatments for the disease. Dillon's vision continued to worsen during his sophomore year. He became despondent. For the first time he struggled at school.

I read about long-term successes in other countries from the procedure known as cross-linking. It sounded hopeful until we learned this procedure was not approved by the FDA. Then we learned about clinical trials in the U.S. for the cross-linking procedure, some with FDA approval.

This prospect was scary at first. Trust me, no parent wants to volunteer a child for a medical procedure called a study or a trial, but we had no

choice. And highly regarded American corneal specialists were heralding the cross-linking procedure, citing the many years of successes elsewhere.

As I read about the fates of other keratoconus patients, including adults who had to quit jobs or couldn't drive or reported dire effects that were irreversible, I knew we had to get the cross-linking procedure for Dillon.

But you can't just go to a doctor and say, put us in your next trial. So we worked to connect with specialists who had done the procedure or were conducting cross-linking trials. We realized Dillon's vision continued to deteriorate; we likely would have to seek treatment outside of the United States.

This was daunting. Without FDA approval, insurance benefits would be limited or non-existent. You can't put a price on your son's eyesight, but still we wondered how we could cover the costs. Then we got lucky. Dillon was offered the chance to be part of an FDA-approved

cross-linking trial with Dr. Rajpal in Virginia.

We sought a second opinion from a specialist at the Wilmer Eye Institute who said we should, "Grab that chance." With keratoconus, a patient's condition can vary from day-to-day. During the trial's initial exam Dillon's left eye was not bad enough to qualify for the study.

It was a tough break. Even after the trial we still would need to find a way to get treatment for the left eye when necessary. Good news came soon after the procedure. Follow-up exams revealed that Dillon's eyesight actually improved, which does not always happen.

He stopped fearing the future. He posted great scores on his college entrance exams and received scholarship offers from all of the universities where he applied. Dillon continues with regular eye exams to monitor the progression of keratoconus, but once again, we are haunted by familiar questions.

Because cross-linking still does not have FDA approval, what is Dillon going to do when he

needs treatment in the other eye? How will this disease affect his career hopes, his future studies, and his quality of life?

I appeal today for your help on behalf of all keratoconus sufferers and on behalf of any parent who one day will hear these dreaded words; "Your child has a degenerative eye disease and treatment successful in other countries has not gained FDA approval."

I urge you to immediately do all that is possible to help people like my son, including reviewing research that has led to cross-linking successes elsewhere. This procedure has a proven track record overseas. Let's use this information to help people now, here in the United States.

Dillon intends to major in criminal justice when he begins university studies next fall. For now, he dreams of protecting and serving others. Won't you do the same for Dillon and those like him? Thank you.

DR. AWDEH: Thank you. Will speaker number 8 step up to the podium and introduce

yourself? Please state your name and any organization that you're representing for the record.

MS. COFER: I'll be reading Dr. Morris Waxler's prepared statement. Additional copies are available in the lobby.

Joint advisory panel members have at least two public health dilemmas. Dilemma A, polymerizing agents may hide a high rate of LASIK-induced ectasia, induced long-term corneal problems, and/or make permanent other LASIK-induced adverse events and visual aberrations.

Panel members are being asked to recommend approval of corneal polymerizing agents without knowing the true rate of LASIK-induced ectasia.

Questions for panel members to consider. Should you recommend approval of a product masking a high rate of LASIK--induced ectasia?

Should you recommend approval of prophylactic polymerizing agents for LASIK-sickened corneas if the true rate of LASIK-induced ectasia is very low, 0.1 percent as claimed by the LASIK

industrial medical complex? Wouldn't treating a large number of LASIK sickened with a low probability of LASIK-induced ectasia have minimal benefit and maximum risk by locking in structural defects causing visual aberrations, haze, halo, and causing unknown long-term problems?

Keep in mind while we do not know the true rate of LASIK-induced ectasia, refractive surgeons and user facilities, manufacturers, keep secret files of LASIK-induced ectasia. I have personally reviewed some of these secret files. I told FDA about the existence of these secret files months ago.

FDA has not asked me for any information about these secret files. FDA appears to have withheld information about secret files from panel members. FDA has been and continues to facilitate an epidemic of LASIK-sickened corneas by false and misleading promotion of LASIK on its website, using a figure falsely showing no dry eyes and night-driving problems one year after LASIK, failing to document the database for this false

figure while dropping it from its website after Dr. Waxler told the FDA it was false, using vague statements about worst case possibilities of LASIK while withholding actual percentages of adverse events -- for example, 20 percent or 4 percent from consumers, using euphemisms for adverse events, for example, complications or systems.

FDA's continuing indifference to the pain and suffering of LASIK-injured patients, for example, failure by FDA to take action regarding nearly 4000 MedWatch reports of LASIK injuries, false and misleading advertising and promotion, corrective and preventative actions to minimize LASIK-induced injuries.

Dilemma B -- what rate of LASIK-induced ectasia is acceptable to panel members? Twenty percent, 10 percent, 4 percent, 1 percent, or 0.1 percent? Millions of Americans have and are going to have LASIK. How many legally-blind people are acceptable to you for a few years of 20 happy vision.

Recommend disapproval. I urge panel members

to recommend disapproval of corneal polymerizing agents until FDA establishes through its control of device manufacturers and user facilities, 1) the true rate of LASIK-induced ectasia, 2) the root causes of LASIK-induced ectasia, 3) corrective and preventive actions to reduce root causes of LASIK-induced ectasia, 4) establishment of a medically and ethically acceptable rate of LASIK-induced ectasia.

FDA, in collaboration with the refractive surgery industry has created a LASIK-induced epidemic of sick corneas. One long-term sight threatening adverse event is LASIK-induced ectasia. The true rate of LASIK-induced ectasia will be buried forever if the panel recommends approval of FDA's plan to approve products polymerizing sick corneas.

FDA leadership on LASIK products has a longstanding collegial and professional bias toward fellow ophthalmic professionals in the industry. They work out many issues in regular private meetings. I know, because I led many of these

meetings and I know of many others.

FDA needs to change its structural prejudice by meeting regularly with LASIK-injured patients. FDA should focus more on public health and not solely on the needs of industry. I urge panel members to send a strong message to FDA. Recommend disapproval of corneal polymerizing agents. Thank you.

DR. AWDEH: Thank you. Will speaker number 9 step up to the podium and introduce yourself? Please state your name and any organization that you are representing for the record.

MR. KOTSOVOLOS: My name is Matt Kotsovolos and I'm going to begin by reviewing four case reports of patients with post-LASIK ectasia, three of whom have had experiences with corneal collagen cross-linking.

Case report number 1 comes from the FDA MAUDE database. The patient states that LASIK eye surgery destroyed his quality of life. Due to his LASIK injuries the person suffers from PTSD and

depression and has been hospitalized for suicidal ideation.

His wife and daughter have also had to endure tremendous pain and suffering watching a once healthy man lose his ability to live life. He goes on to state, "We have no idea how precious our eyes are until they are destroyed."

His story is heartbreaking, but it's just one of tens of thousands. The patient goes on to ask a question to the FDA. He states, "What is the FDA doing about this issue that they have known about for a decade? Why have they not responded to Dr. Morris Waxler's formal petition calling for an end to LASIK?"

Has the FDA, at a minimum, ever issued a public health advisory on the risks of LASIK such as ectasia? The answer is no. Instead, the FDA finds it acceptable for thousands of Americans to have their lives destroyed by an unnecessary surgery and feels it has done its job by simply updating the FDA LASIK website.

The FDA also caters to the LASIK industry

while treating injured LASIK patients as merely collateral damage. The latest example is the FDA downplaying the results of the PROWL studies.

For case number 2, a woman in Minneapolis who was placed in the Avedro clinical trial. She states that CXL has taken the vision from her eye and rendered it useless. She was to be followed up for two years, but was abandoned by her physician.

Ectasia patients are vulnerable since they are attempting to cope with a sight-threatening disease. It would be devastating for these patients to be given hope of a cure through false advertising and then abandoned by the physician when the reality sets in that CXL on post-LASIK eyes is less effective than on keratoconus eyes.

For case number 3, a woman diagnosed with corneal ectasia had cross-linking in one eye. The treatment failed. One year later she had Intacs implanted in the same eye which made matters worse. She is now being advised to have corneal transplant.

It is imperative that if CXL is approved,

only cases with documented evidence of progression of the disease should receive treatment. If not, you will get cases like this one where the physician was advising cross-linking on a patient who clearly did not have progression of a disease.

The current application states that progression needs to be shown for keratoconus, but it makes no mention of progression for ectasia. This oversight must be corrected or ectasia patients will undergo unnecessary CXL procedures with many risks.

Eye doctors continue to wear glasses, even with the most current technology. Those with inside knowledge of the real risks know to stay away from refractive surgery. I'd be surprised if those within the Ophthalmic Division of the FDA are getting refractive surgery since they're also part of the exclusive club knowing the real risks of LASIK.

When it comes to LASIK, the FDA Ophthalmic Division treats the public as if it were the lowest social class. The FDA sees no need to inform the

public of the risks of LASIK, despite evidence of the carnage all around them.

In fact, there is evidence before us today as we discuss a therapy to treat post-LASIK ectasia, a sight-threatening condition brought on by the LASIK that affects thousands, if not tens of thousands of patients.

The LASIK industry has done an impressive job of keeping a lid on the growing epidemic of corneal ectasia. The future is LASIK Xtra which is LASIK with cross-linking. I urge the FDA to close the door on LASIK Xtra before the technology is unleashed.

I recommend that CXL be disapproved on the basis of the following: Post-LASIK corneal ectasia is occurring at a much higher rate than the industry has led the FDA and the public to believe. An unnecessary surgery such as LASIK that is associated with frequent destruction of life should not have the FDA's stamp of approval.

DR. AWDEH: Thank you. Let's move on to speaker number 10. Can you please step up to the

podium and introduce who you're speaking on behalf please?

DR. KOTSOVOLOS: My name is Matt Kotsovolos and I will be speaking, presenting, on behalf of Michael Patterson.

LASIK physicians engage in one of the most unethical medical marketing practices in the U.S. They know that they can advertise LASIK as risk-free because they operate with impunity. CXL has already begun to marketed in a LASIK-like unethical manner as shown by this leading LASIK surgeon's website.

The CXL process includes radiated light to the eye for 30 minutes with the riboflavin solution amplifying the effect of the light on the corneal tissue. There's a long list of risks associated with CXL. It should be made clear to patients that the goal of CXL is to halt progression of corneal ectasia. It does not cure the disease or reverse the damage.

CXL on post-LASIK eyes is less effective than on keratoconus eyes. Much of the treatment

effect is lost on the LASIK flap which is permanently decoupled from the underlying cornea and therefore provides no biomechanical strength to the cornea.

Visual outcomes of CXL in patients with ectasia are inferior to keratoconus patient outcomes. It should be emphasized that the window of opportunity to benefit from CXL is very small, since patients over 35 years old experience more complications and receive less benefit.

However, the FDA cannot leave this to the refractive surgeon industry to disclose. Refractive surgeons have proven that they cannot police themselves. With CXL, the FDA has an opportunity to get required patient labeling right, before approval and release to the public.

The International Agency for Research on Cancer classified all categories and wavelengths of ultraviolet radiation as a group 1 carcinogen. This is the highest level designation for carcinogens and means, "there is enough evidence to conclude that it can cause cancer in humans."

In fact, in an article in Eye World, Dr. Bill Trattler speculated that the delay in approval could be related to the wavelength used in the device, possibly leading to cancer in 10 to 20 years. If approved, will the FDA stipulate that patients receive a copy of the patient labeling? Or will the agency be complicit in denying patients information they need to make an informed decision, as it did in 2006 when the patient labeling mandate was quietly dropped from laser approval letters.

The Belmont Report describes the rights of human subjects and the ethical basis of informed consent and it's clear that, "Avoiding harm requires learning what is harmful." That did not happen with LASIK. The clinical trials did not provide honest, empirical research intended to distinguish issues considered to be side effects from those considered adverse effects which resulted in real suicides.

Let's not forget that one of the original applicants for LASIK approvals was Summit Technologies, later acquired by Alcon. The driving

force behind Summit was David Muller. Is the FDA being led down a similar path today with corneal collagen cross-linking?

Did Avedro learn what is harmful? Did the Avedro studies ignore quality of life issues as the Summit Excimer Laser trials did? Once a technology is in the hands of refractive surgeons, they won't hesitate to use it off-label.

A perfect example is LASIK enhancement surgery. The indications for CXL being proposed today pave the way for LASIK Xtra, Avedro's riboflavin UVA light treatment as an adjunct to standard LASIK. It will be deceptively advertised as a way to make LASIK safer.

If LASIK isn't safe, it shouldn't be performed at all. If cross-linking is approved, the FDA should place a black box warning to prevent its misuse. I recommend disapproval of CXL to the panel. CXL will be marketed as a miracle procedure by the industry despite clinical data showing significant efficacy limitations.

Once the FDA puts CXL in the hands of

dishonest refractive surgeons, the FDA will ignore false advertising, non-reporting of adverse events and injuries. The only recourse for patients who suffer injury from CXL is the legal system, but refractive surgeons have built an impenetrable white wall of silence to stymie malpractice lawsuits. Thank you.

DR. AWDEH: Thank you. Will speaker number 11 step up to the podium and introduce yourself, please?

DR. SMITH: I am speaking for Roger Davis, though I am not, myself, Roger Davis. As far as I know he has no relevant financial considerations or institutional affiliations.

These are Dr. Davis' words.

Panel members, in 2008 I presented data to the Ophthalmic Devices Panel about an epidemic of depression and suicidal ideation caused by LASIK. Among 46 patients in our study admitting to suicidal ideation, 48 percent described dry eye, 39 percent described dim light and night vision problems. Eighty-three percent of those patients

said they were referred to as a success by their surgeon.

This is from the complications of refractive surgery study that was completed while I was research director of the Surgical Eyes Foundation, a non-profit created to help victims of the LASIK industry.

Other patient advocates at that meeting presented actually suicides. One parent described the suicide of his son. After the 2008 hearings, damaged LASIK patients wondered why this epidemic continued to go unaddressed by the FDA. The community continued to deal with the depressed and suicidal patients as best we could.

In 2010, we got an explanation. Dr. Morris Waxler, the FDA's chief research scientist during the LASIK clinical trials came forward with evidence that rates of dry eye and higher order aberrations were covered up by industry.

Before its official approval, Dr. Waxler claims, LASIK was already widely used off-label, a practice the FDA wanted to reign in. In an

interview with website Medical Marketing and Media, he says that the FDA "made deals" with the LASIK industry that "degraded the scientific quality of the collection and analysis of adverse event data of LASIK devices."

Waxler listed alleged deals with the following entities -- Kremer Laser, American Society for Cataract and Refractive Surgery, CRS Inc., and more than 100 user facilities that he says received IDEs "to study LASIK in order to minimize their exposure to violating off-label rules."

Dr. Waxler should know. He represented the FDA in those deals. To assess the scientific foundation of Dr. Waxler's claims, I analyzed cases from the MDR reports for LASIK. Since the efficacy of LASIK is not in dispute, I focused on depression and suicide as these are relevant to safety and approval requires both effectiveness and safety.

From 2001 to 2011 a total of 67 cases were identified as mentioning depression and/or suicidal ideation. Among these, 63 percent mentioned dry

eye, 37 percent mentioned night vision disturbances, and 36 percent mentioned higher order aberrations.

Now if dry eye, night vision issues, and HOAs are simply side effects, we would expect no association with depression and suicide. We would expect that depression and suicide would only be associated with adverse events. Only 3 of the 67 MDR reports were filed by manufacturers. The rest were filed by patients.

How many were filed by surgeons? Zero. These public data replicate the core study and support Dr. Waxler's claims that dry eyes and HOAs were classified as side effects to obtain approval. FDA guidelines state that adverse events should not occur in more than 1 percent of patients.

Finally, surgeons apparently do not report bad outcomes when the patient wants to die. Either that, or surgeons do not understand that depression and suicide are relevant to safety. Well the same thing happened with cross-linking.

Thank you.

DR. AWDEH: Thank you.

DR. SMITH: Okay. I am actually speaker number 12.

DR. AWDEH: Great. So let's --

DR. SMITH: My name is Richard Smith.

DR. AWDEH: Thank you.

DR. SMITH: I have no relevant financial associations with the proceeding today and no relevant institutional affiliations. I'm a clinical psychologist and like some others speaking this hour, my eyes were damaged by LASIK. Now what are we LASIK casualties doing here? Why are we here?

Well for one thing, we get nervous about new treatments to help eyes as we know how destructive such help can be. Furthermore, we know today's events will influence future evaluation of another procedure -- LASIK plus corneal cross-linking or CXL.

Every year, upwards of 6000 Americans are newly diagnosed with keratoconus. By contrast, every year roughly 600,000 Americans get LASIK.

Numbers tell the story. If CXL is approved, it's likely to become an off-label and questionable safety warranty tacked on to many of those LASIK procedures. That's where the biggest market lies.

Although CXL may arrest keratoconus and ectasia, its risks to eye health are significant. Someone facing severe eye deterioration might embrace those risks, but to add them to the known risks of LASIK, a medically unnecessary surgery, flies in the face of the ethical dictum to first do no harm.

I urge that any approval of CXL not open the flood gates for its off-label marketing as an add-on to LASIK. Otherwise, future approval of the combo procedure could become a foregone conclusion. That kind of thing has happened before.

In the 1990s, by the time the FDA greenlighted PRK, an earlier refractive surgery, LASIK was the hot new thing. Many surgeons performed it, without FDA sanction, using lasers approved only for PRK.

According to Morris Waxler, then branch

chief of the Center for Devices and Radiological Health, agency officials got worried that LASIK's unregulated spread would weaken the FDA's reputation by exposing its inability to restrict approved devices to approved uses.

So to keep surgeons under at least nominal government oversight, the agency fast-tracked approval of LASIK. Predictably, this rushed job was a botched job. For one thing, according to Waxler, the FDA allowed industry too much say in establishing definitions of safety and effectiveness.

I learned firsthand how inadequate those definitions were. After LASIK, I passed a key test by correctly reading the 20/20 line on the Snellen eye chart and my eyes showed none of the gross damage officially designated as adverse events.

For me, LASIK counted as safe and effective. The reality, I could read that 20/20 line, but my entire visual field was blurred. Far worse, LASIK triggered a dry eye condition so painful that for a year-and-a-half I often wanted to be dead, but by

official definition I had not experienced an adverse event, just complications and side effects.

Now some advisory committee members voiced caution about LASIK back then. During a 1999 hearing, Frederick Ferris of the National Eye Institute acknowledged it was bizarre to debate approval of the surgery already in widespread use.

He reported that during his drive to the day's meeting he'd heard, "a number of advertisements for this procedure." I thought to myself, well, people little note nor long remember what we do here, because as near as I know this train is moving.

Learn from this history. If you approve CXL, stipulate that it cannot be marketed to supposedly boost LASIK safety. Stipulate that any promotion of it for unapproved uses will constitute misbranding. If you don't, when the LASIK CXL application comes before you, you may end up in a situation where the only tool you have is a rubber stamp. Don't let that happen. Thank you.

DR. AWDEH: Thank you. Will speaker number

13 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. COFER: I'll be reading a prepared statement by Dr. Edward Boshnick, optometrist in Miami, Florida. I have been in private practice for 45 years and before that for two years in the U.S. Army Medical Service Corps.

My practice for many years has been limited to a specific patient population, mainly patients who have experienced loss of vision due to refractive eye surgeries such as LASIK and radio keratotomy, keratoconus, corneal transplant surgery and so on. Over the years, I have taken care of thousands of keratoconus patients.

In addition, I have also taken care of several thousand patients who have lost vision due to post-LASIK ectasia and other complications due to LASIK and other refractive surgical procedures. Avedro has a financial interest in the corneal collagen cross-linking controversy.

I have no financial interest in this

industry, so I will write what I consider to be the truth as I know it. Keratoconus is a genetically determined condition that is progressive in nature. However, the progression is not open-ended. By that I mean that the condition has a beginning and an end.

Usually the active period lasts for about five years. I can understand that a patient, especially a child who is recently diagnosed with keratoconus, may face a number of years with the possibility of progression.

I think that in such cases, cross-linking may be a viable option to consider. However, in an adult who has had to deal with keratoconus for many years, it may not be a realistic choice. Again, over the life of a keratoconic patient, the corneal topography will exhibit minor changes, whether or not cross-linking is done.

This is normal. Very rarely will I have to make changes to a contact or scleral lens design due to progression in an adult patient. However, small changes to the corneal topography may lead me

to change a contact or scleral lens design. Again, small changes over time to the corneal topography and ocular surface is normal over time, regardless if cross-linking is done or not.

Corneal ectasia is a different matter entirely. LASIK is a procedure that thins out the cornea. A normal cornea is about 550 microns thick. After LASIK is done, the corneal thickness may be reduced to 350 microns or less. Over a period of years, the pressure from inside the eye against this weakened corneal wall can cause the cornea to buckle or pop. We call this ectasia.

It has been my experience that this takes place rather suddenly with an active period that can last several weeks to several months. The great majority of patients who I have seen with ectasia have relatively stable corneas for many years following the onset of the condition.

In addition to my patients with ectasia who did undergo cross-linking, have corneal topographies very much the same as their topographies before cross-linking was done. Again,

because we're dealing with soft tissue as opposed to bone, it is normal for small changes to take place in the corneal topographies and on the ocular surface over time.

Please understand that the comments and observations above are mine and based on what I have seen in experience. I did not do any controlled studies involving progression on any of my patients with keratoconus or ectasia.

I must add that the emotional impact of surgically-induced corneal ectasia is often quite severe. Many of my patients have expressed thoughts of suicide. These are patients who had healthy eyes with good correctable vision before being sold an unnecessary refractive surgery.

The FDA must ensure that cross-linking will not be misrepresented to these patients as a treatment that will undo the damage. I suggest that the panel recommend limiting the product to cases with active progression and include all applicable risks, precautions, and warnings in the labeling to be given to patients so they can make

an informed decision. Thank you.

DR. AWDEH: Thank you. Will the final speaker, speaker number 14, step up to the podium and introduce yourself, please? State your name and any organization that you're representing for the record.

MR. KOTSOVOLOS: My name is Matt Kotsovolos, and I will be presenting on behalf of Dean Kantis. Dean's vision was ruined by David Muller's Summit Technologies Apex Plus laser that the FDA approved.

In the 1990s, the American investigator TV series exposed David Muller as having contributed huge amounts of money to Ted Kennedy's re-election campaign in exchange for political access. Summit Technologies was later sold to Alcon for $90 million.

A core question to be asked is do you believe the industry is honest with you here today? Panel members, consider the transcript that I'm about to read from a conference at a top 10 eye center in the U.S.

The transcript reads as follows: "I guess

in the fall about two years ago, we had 19 cases of kerectasia, 2800 eyes, 1400 patients. We excluded, I think there was like 8 of them, they said, were formed through keratoconus, but one-third of those 19 eyes had a corneal bed thickness, residual stromal bed thickness of greater than 250 microns.

"None of them more than 300 microns. None of them more than 8 diopters of correction, but if you extrapolate, you know, if you went purely with the data, it would be 0.67 percent incidence or almost 1 percent.

"And if we look at our own practices, I think the kerectasia incidence is a lot higher, just like you alluded to, but it's not being reported, because of the litigious natures of what's going on, and a lot of us obviously don't report it because these patients are being referred in to us.

"So I thought for fun I would love to ask the audience how many of us have more than 5, more than 10 cases of kerectasia in our practice, just for our own general interest. It would be

interesting since a lot of us have a full practice. It would be fun to find out."

I'll repeat sections of the transcript for emphasis. The speaker states, "I think the kerectasia incidence is -- it's a lot higher, but it is not being reported because of the litigious nature of what is going on and a lot of us do not report it, so I would love to ask the audience how many of us have more than 5, more than 10 cases of kerectasia in our own practices. I would love to find out. It would be fun."

The video suggests four points. Point number 1, the industry is once again duping the FDA; this time about the true incidence rate of ectasia.

Point number 2, surgeons do not report adverse events, thus violating federal law, as patients have always claimed. Ectasia is an incontrovertible adverse event.

Point number 3, industry is content to let 0.67 percent rate stand as science, as this rate supports their claim about the safety of LASIK.

And point number 4, surgeons discuss the truth amongst themselves and they are not telling the public or the FDA about the true rates of complications.

Dr. Morris Waxler, former head of clinical research trials at the FDA stated that refractive surgeons and user facilities keep secret files of LASIK-induced ectasia. Dr. Waxler told the FDA about the existence of these secret files months ago.

The FDA has not asked him for any information about the secret files. I will revisit this point later, but for now, I will point out that LASIK surgeons have grown completely accustomed to operating with impunity.

The only way to stop this pathological behavior where LASIK surgeons treat patients as eyeballs, rather than people, is through a criminal investigation.

Morris Waxler stated the FDA does not want to admit that millions of people have now had a surgery that never should have been approved by its

own rules. The FDA is now engaged in a LASIK cover up which should prompt a criminal investigation into those responsible for falsifying the LASIK safety studies.

In conclusion, we need a criminal investigation initiated by an unbiased agency outside the FDA. I ask the media to urge Congress to issue a federal criminal investigation into those FDA directors of ophthalmology, the pawns, and for this physician and medical company entrepreneurs that know how to sidestep safety data through FDA approval processes that are responsible for abusing their powers and inflicting permanent injury on the very citizens paying them for their protection. Thank you.

DR. AWDEH: Thank you. I'd like to thank each of the public speakers. The open public hearing portion of this meeting is now concluded.

Questions to the Committee and Discussion

DR. AWDEH: Thank you.

I'd like to thank each of the public speakers. The open public hearing portion of this

meeting is now concluded, and we will no longer take comments from the audience.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before this committee, as well as the public comments just made.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

For that, we'll start with discussion question number 1. I will read the question for the record, and then open it up for discussion. Please discuss and comment on the following study design elements, Planned Enrollment and Size of Studies; 160 patients, 80 per arm originally planned in the studies below versus actual enrollment.

Bullet point 2, size and safety and effectiveness database in UVX-001 and 002

progressive keratoconus, CXL group 102; sham, 103; and in the UVX 001 and 003 corneal ectasia, CXL group 91 and sham, 88.

I'd like to open this question to the panel, and let's start it with the item of a 160 patients per arm in the originally planned study size. Can we pull up the slide?

We're going to pull up slide 39 from the FDA presentation earlier. To the members of the panel, does anybody have a concern regarding the planned number of participants in this trial versus the actual number randomized in UVX-001? Dr. Belin?

DR. BELIN: Could we add to that slide how many of those -- I mean, the anticipated originally was the 160. They didn't reach it. How many of those that were enrolled completed 12 months data?

DR. AWDEH: How many of the 58 and 49 randomized patients actually completed 12 months of data?

DR. BELIN: It was a little over half is my recollection. That's why I just want to check on that.

Is that correct? My recollection, it's slightly over half. Is that --

DR. AWDEH: Does someone from the FDA want to clarify that question?

DR. ZHUANG: This is Dongliang Zhuang. Can we go to slide 43 and 44? Look at 43 for progressive keratoconus first. Is this the number you're looking for? So at 12 months, 20 in the CXL group complete 12-month study and also 20 in the sham group for 001.

DR. BELIN: So 92, if you add UVX-001 and UVX-002?

DR. ZHUANG: Right.

DR. BELIN: Twelve month complete, you have 20 and 72, right? So 92 total?

DR. ZHUANG: Yes.

DR. BELIN: So 92 total of the original anticipated 160 completed 160 completed the study to the 12-month point, even though originally, it wasn't a 12-month study.

DR. ZHUANG: These results are provided by the applicant. We haven't got a chance to verify

these results yet.

DR. BELIN: The other thing that wasn't discussed at all with the protocol violations or failure to follow protocol, which seemed extremely high for a study. I'm wondering if the sponsor can comment on that.

DR. AWDEH: Could we ask the sponsor to comment on protocol deviations, please?

MS. NELSON: Pam Nelson, vice president of regulatory affairs for Avedro. So yes, we did take a close look at the protocol deviations. Now, keep in mind that the list includes the deviations for all eyes, including the randomized study eyes and the secondary eyes.

The majority of the deviations were minor. All but two deviations were minor, and that included one group that was randomized to the cross-link, that got treated in one group that was randomized to the control group that was subsequently cross-linked.

So approximately 2.7 deviations related to patient consent. All patients consented prior to

receiving the treatment. However, there were some standard of care procedures that were conducted. And again, we took a very conservative approach when looking at these deviations and did a complete evaluation.

Again, 95 percent of those deviations were minor and related to study procedures now performed, such as a missing of an IOP measurement or missing a study visit window by a few days.

DR. BELIN: Maybe we're calling it something different. Let's take cell counts. Weren't cell counts part of your protocol?

MS. NELSON: Yes. Endothelial cell counts were part of the protocol, and measurements were required at 3 months and 12 months.

DR. BELIN: How many patients had them at 3 months and 12 months?

MS. NELSON: The majority of the patients had endothelial cell count data at the 3-month and 12-month protocol.

DR. BELIN: Majority meaning 51 percent or --

DR. HERSH: We'll get that number for you.

MS. NELSON: Right. We'll just need to get that for you.

DR. HERSH: It's about 80 percent.

MS. NELSON: I'll defer to Dr. Hersh, who has a more detailed figure on that.

DR. HERSH: I believe there were 66 eyes in one study group and 62 eyes in the other study group that had a consistent cohort that we evaluated. The N numbers at zero, 3 and 12 were larger, but the consistent cohort in the keratoconus group was 66 eyes and the ectasia group was 62 eyes. And this was only looking at the randomized studied eyes.

DR. BELIN: So about a third did not happen, if you had 92 and you had something, roughly. I have a problem only that what we're being told -- and when I was looking over this paperwork, I found a deviation of about a third of the people didn't get their cell counts. Not that that's a big thing or not, but then when we're told we have a 2 percent deviation rate, which doesn't jibe with

a third of the people not getting their cell counts, about a third did not maybe get IOP measurements.

It just seemed to be a lot of protocol violations that don't show up on your slides of deviations, and would like that explained.

MS. NELSON: To clarify in terms of the protocol deviations and subjects, yes, you're correct that there is a number of protocol deviations. But again, when we looked into that, the 2.7 -- this is regarding one category. But overall, 95 of them were minor in terms of study visit procedures. But again, all patients consented prior to treatment.

DR. AWDEH: Yes, go ahead. Dr. MacRae.

DR. MacRAE: Dr. MacRae. In terms of the conformed consent, can you enumerate a little bit about that. What was that? What was the problem with the 2 percent that had an inadequate informed consent or some kind of problem with informed consent?

DR. HERSH: As an example -- I don't have

the numbers in front of me -- patients needed to initial every page of the informed consent. So if one page was not initialed, that was a protocol deviation. If any study related testing was done before signing an informed consent -- you got a K reading before you signed an informed consent -- that was deemed an informed consent issue. So they were all, for the most part, something like that.

DR. MacRAE: They were all consented, but some of the procedural

DR. HERSH: Right. Everybody was consented for the study. There were these minor deviations.

DR. MacRAE: Thank you.

DR. AWDEH: I don't know that we fully answered the first question, and I think Dr. Belin had gotten into it. So regarding the 160 patients, 160 were planned versus actual enrollment. That means for 001, 320 patients were planned; 160 in the progressive keratoconus group; 160 in the corneal ectasia group. What was actually enrolled was 58 and 49.

The question is to the committee is to whether this size is acceptable or not.

Dr. McLeod?

DR. McLEOD: So I think there are a couple of questions that I would have. The big question really is whether or not it's just a matter of not getting the numbers that would allow you to say with assurance what your power is versus whether or not there was relatively a low rate of enrollment and was there a defined enrollment period at which time you sort of ran the clock out and didn't enroll anymore. Or was it a matter of the data being looked at a certain point in time in the context of a relatively low enrollment; because obviously, the issue of looking at the data is what will drive it away from just low power to corrupting the analysis.

DR. AWDEH: Dr. Leguire?

DR. LEGUIRE: Larry Leguire. Reducing the N would have nothing to do but reduce the power and reduce the probability of finding statistical significance. Given that this is an orphan

product, I'm not surprised that they undershot their planned number simply because these patients are hard to recruit. There's not that many. Regardless of what we hear today, there's not that many out if it's an orphan product designation.

I think the most important thing is what findings did they find with the patients they did have, not that they didn't reach the plan number. I think that's a very minor, almost -- just almost insignificant. What we really have to look at is what the result show given the numbers.

DR. AWDEH: Dr. Belin?

DR. BELIN: I would like the FDA to clarify something. My understanding is we as physicians think orphan means that it's a very rare disease. That's clearly not the case in keratoconus. I think that was just an orphan application because it's meeting an unmet need, which is different than a disease that affects less than 10,000 people.

This is very common. Keratoconus is, as you heard, 1 in 2,000, which is probably grossly underestimating the true prevalence of the disease,

something we see routinely in all practices. But can someone address that from the FDA?

DR. CHAMBERS: This is Wiley Chambers. The application has -- the applicant did request orphan designation and was granted orphan designation for each of the two indications. Orphan designation means there is less than 200,000.

DR. AWDEH: Dr. McLeod?

DR. McLEOD: I still actually would like an answer to the question as to whether or not the data were looked at before the end of the defined enrollment period.

DR. MULLER: Sorry. The question was looked at -- one more time, please. David Muller.

DR. McLEOD: So the question is at what point in time were the data looked at? In other words, was a decision made to halt enrollment before or after the data were examined?

DR. MULLER: Right. I guess a little explanation again on the study. The original sponsor of the study was a small German company, and he ran out of money, and the study stopped. So

the study was really -- when we were able to essentially purchase the study and the data, the study was already closed. Patients were no longer being enrolled, and all patients that were to be treated were treated.

So when we purchased the study, we had no knowledge of what went beforehand. There was the publication from Dr. Hersh's single-study group that was published. But again, that was after all patients were treated and after the study was stopped.

DR. OWSLEY: Could I ask a follow-up on that?

DR. MULLER: Sure.

DR. OWSLEY: Before you agreed to purchase the data, did you look at the data?

DR. MULLER: No.

DR. AWDEH: Dr. Corcoran?

DR. CORCORAN: That was the question that I had, was it seemed like the study had finished and wasn't planned. That wasn't the enrollment that was planned. It had some other outcome. That was

what I wanted to know.

DR. AWDEH: Dr. Weiss?

DR. WEISS: I would respectfully disagree with Mr. Leguire, is that you do need a certain number of patients to reach statistical conclusions. And I would think most of us would imagine in the period of time the study was done, there would have been that difference of patients available to bring it up to 160.

So clearly, there were challenges in getting those patients. But we've heard about the number of patients with these conditions, and they certainly are out there.

I'm still a little bit confused in terms of the 160 per arm that were needed and then adding that to Dr. Belin's question of the percentage there that had follow-up, because that bottom-line number for each of those groups will tell us who was available. And then I would end up bumping that to FDA, from a statistical standpoint, is there enough power in this? Because it's really a statistical question as opposed to just a

subjective judgment question.

DR. ZHUANG: This is Dongliang Zhuang. I think the first thing is that the number of subjects per arm is 80 subjects. It's not 160 subjects.

DR. AWDEH: Can you speak into the microphone, please?

DR. ZHUANG: The number of subjects per arm is 80 subjects in each study. It's not 160 subjects, just to clarify.

DR. AWDEH: Let's talk about the slide that's on the screen right now. This is a slide that we're all looking at.

DR. ZHUANG: Right. So for two indications -- in study 001, you have two indications. Each indication is 160 subjects. There are two arms, so each arm is 80 subjects.

DR. AWDEH: Correct. So take the column for progressive keratoconus. Out of the 160 planned patients, 80 were planned to be in the treatment group and 80 were planned to be in the control group.

DR. ZHUANG: Right.

DR. AWDEH: And out of those 80, 29 ended up in the treatment group; 29 ended up in the control group.

DR. ZHUANG: Right, that's correct. What's the second part of the question?

DR. AWDEH: I think the question that Dr. Weiss is asking back to the FDA, is that number, 29 and 29 that actually ended up to the total of 58, is that number adequate from a power perspective for the study? Is that correct?

DR. ZHUANG: We look at the power before the study starts. Usually we don't use the power of a study after it's finished. I don't know how to answer this question.

DR. WEISS: Jayne Weiss again. Let's say we have 29 patients in 001 who have had the cross-linking. Ideally, you would have had 80. We also have for similar condition, in 002, 73 patients, ideally, you would have had 80. If you pooled those two, only those patients who have had the 12-month follow-up, even though the power

considerations were for the larger number, do you take away -- is there --

DR. ZHUANG: I would like to --

DR. AWDEH: Is there someone else in the FDA who would like to respond?

DR. WEISS: It sounds like there's an answer coming.

DR. AWDEH: Go ahead.

DR. WANG: My name is Yan Wang. I'm the statistical team leader for this NDA review. So to answer your question -- I think your question you asked is whether there is enough power to detect efficacy results and the safety results.

Can you phrase your question again, and I'm going to answer your question.

DR. WEISS: So if we pool progressive keratoconus between 001 and 002, and only include those who have had 12 months follow-up with the cross-linking, and we also pool ectasia 001 and 003, and only include the patients who've had 12-months follow-up with the cross-linking, is there enough data to establish safety and efficacy,

in terms of power? Is there statistical power?

DR. WANG: Right. When we design the study, we only talk about power to detect treatment effect for efficacy purpose. So the study was not planned to power to answer safety.

DR. WEISS: So tell me about efficacy, then. Is there enough power to detect the efficacy?

DR. WANG: For the efficacy power, the sponsor states that they're assuming they have the treatment difference 1 unit, 1 diopter and the standard deviation is about 2.5 diopter. So based on these assumptions, 80 subjects per arm will have a power about 80 percent.

We only talk about study power when we design the study. Once the study's finished, we don't talk about power in that sense. In terms of safety, normally we want to have about -- at least 300 people treated so that we can detect an adverse event, at least 1 percent.

DR. WEISS: So we don't have 300 people treated.

DR. WANG: Right, in that sense.

DR. WEISS: So from an FDA standpoint in terms of what you apply to most studies, we do not have the 300 patients treated that you would need to establish safety.

DR. WANG: Right.

DR. WEISS: And then in retrospectoscope, if you had these numbers and you went forward and did a study -- sorry.

DR. AWDEH: I'm getting a lot of head nods, so can we clarify that comment, please? Dr. Chambers?

DR. CHAMBERS: Yes. The 300 number is the number that statistically you would need to be able to detect a 1 percent adverse event rate. So the lack of -- the fact that you don't have 300 patients means that adverse events could occur more frequently than 1 percent, and they wouldn't necessarily show up in the trial.

What the FDA is asking you right now is with the database that is available, is this sufficient, recognizing you would not detect low adverse events. But we're asking you is that acceptable in

this case or is that problematic in this case.

DR. WANG: I have one more clarification. Those 300 subjects is to detect adverse event of 1 percent, not more than 1 percent. So if you have adverse event occur at a 1 percent rate, you could not detect that with less than 300 subjects.

DR. AWDEH: Thank you.

Dr. Weiss, are you satisfied with that answer?

DR. WEISS: Yes. I'm going to go off script and maybe say something I shouldn't, but it's sort of the elephant in the room. As corneal surgeons, I think many of us would like cross-linking, and the rest of the world has cross-linking. And everyone asks why does the United States don't have cross-linking.

Then as members of the panel, we're being asked to look at this particular study, and this particular study is abysmal. We're being asked to approve a machine for which there's no data for the machine. It's all theoretic. And if we could do everything on theory, we wouldn't have to have

PMAs, and everyone could save a lot of money.

So we're asked to look at this machine with a smaller 9 millimeter, which we have no data on. We don't have the number of patients enrolled that were asked to be enrolled. We have a lot of protocol deviations, and we don't even have the same time point for the people who didn't have the treatment who did have the treatment. And yet, I think a lot of us feel that --

DR. AWDEH: Dr. Weiss, hold on. Let's just --

DR. WEISS: I'm off script. Sorry.

DR. AWDEH: We've got a territory to cover --

DR. WEISS: Yes. Sorry.

DR. AWDEH: -- so let's focus on -- the question that I'm asking this panel is, back to the size, is there a comfort with the size or not? And it came back to clarify. So let's go back to Dr. Belin.

DR. BELIN: It's a question that you really can't ask that way because the question -- as Jayne

started talking about -- talks about both safety and efficacy. I'm willing to accept a higher or a lower safety profile because we're dealing with disease corneas that really have -- the options after that are more invasive.

My concern on the efficacy variable is I think it's a very poor efficacy variable they looked at. And they had other data that could have been looked at. So to me, Kmax is one endpoint. It's not a very good endpoint. And I don't know if this is progressive keratoconus or it stabilizes it. I don't know if the cornea is further getting ectatic on the posterior surfaces, a lot of other things that weren't looked at -- looked at one variable.

DR. AWDEH: A few questions down, we will get to other variables, and we can discuss that.

DR. BELIN: So it's difficult to answer the question about is the number okay when I don't think the variable's okay.

DR. AWDEH: Dr. Huang?

DR. HUANG: I'd like to stick to the

question number 1. I think we are charged with a mission, if this is a good number or not good number for the various of the study. In direct answer to Dr. Belin's previous comment, I guess he's asking the reliability of all this in the endothelial count, has there been follow-up quickly.

I believe the FDA provided some data, and I just did a quick tabulation. If you compare pages 39 and 40 and combine the upper two tables and the lower two tables, out of the progressive keratoconus, the cross-linking one or two patients, actually there were 94 in the initial endothelial count. At 3 months, there are 86. At 12 months, there are 80.

So that's the question. It's about 80 percent follow-up. And in the control arm, you started with 103. You have a 94 as the endothelial count. And then at 3 months, you have 91. Unfortunately, at 12 months, because of the crossover, you have zero endothelial count in the crossover.

Then in the progressive -- I'm sorry. In the cornea ectasia induced, you started with 91 patient, and then 87 of them have the endothelial count. At 3 months, they are 77. So again, it's about 80 percent of the endothelial count. And then by the 12 months, they are 60 percent.

So we are close to 60 percent of the endothelial count in terms of the follow-up in the treatment group. Then in the so-called control group, keeping in mind they are crossover, it started with 88. And then in the beginning, you have 81 endothelial count, 77 at 3 months, endothelial count. Unfortunately, at 12 months, you only have 2.

So the study itself, I think -- it depends on how you want to -- if you want to look at 12 months, in the treatment group, you have sufficient data, in my mind, to analyze some of the questions raised.

DR. AWDEH: Okay. Thank you. I will try to -- Dr. Sugar?

DR. SUGAR: I would like to agree with that

and say that if we look just at the pooled data, we do have 80 percent power to detect the 1 diopter difference, and therefore we meet the standard if we use just the pooled data. And the conclusions are I think appropriately based on the pooled data.

DR. AWDEH: Thank you. Dr. Belin?

DR. BELIN: I'll get off this subject after this next comment. I think we're putting, whichever's inappropriate, the cart before the horse. If this was an oral hypoglycemic agent, and I came out with a drug, and I said, look, I'm showing you that this lowers blood sugars by 20, and my conclusion is it's effective in preventing progression of disease, you'd say, look. You haven't looked at kidneys. You haven't looked at peripheral vascular disease. You haven't looked at diabetic retinopathy. You're just lowering blood sugar by 20. You can't make that conclusion.

We're asking to validate a number when we haven't yet validated its validity of the endpoint.

DR. AWDEH: The comment is taken. Let me try to summarize what this panel has just said,

which is the following, that there is comfort with a number of patients put together into the pooled data. And with regards to UVX-001, there is still a question mark as to whether the number of patients that are randomized here is adequate.

Is that correct? Someone who's not spoken, would someone else like to join the conversation? Dr. McLeod?

DR. McLEOD: I don't think we actually addressed the question of whether or not the numbers were adequate. I think the challenge is that it does bring a bit of a judgment call into it because that 1 percent that could be a bad event is undefined. It could be something we haven't thought of.

So the question is, then what is the probability that in the context of a keratoconus population that we recognize we're going to have a subgroup where things go badly over time, that some event could happen that's actually worse than having cross-linking at some point in time. And that's a judgment call for which we have no data.

I would say, though, that given the fact that we are dealing with a group of patients, at least some of whom in this group probably did have progressive disease, that the size at least allows us to acknowledge that. There aren't dreadful complications associated with this, and that's consistent with international data.

It would have been helpful to have more detail. If you look at what the most common complication reported there is, that being corneal haze, given the fact that has long been recognized as a potential issue, it would have been nice to have data on the grading and staging of haze. It would have been nice to have data that correlated, if the correlation exists, the amount of haze and change in acuity, or other measures of vision function, but we don't really have those data.

That said, the catastrophic things we would worry about seem not have presented themselves, and this is a population that has real disease.

DR. MacRAE: Can't we ask for that data? Can't the sponsor provide that to FDA?

DR. AWDEH: We will have that opportunity a few questions down the road. Dr. Feman?

DR. FEMAN: Well, I am concerned with -- I think Dr. Belin raised a question earlier about adverse events. And some of them were described as adverse events or kind of insignificant, like the intraocular pressures are measured on the wrong date.

How do we know they're insignificant? Why were you measuring them in the first place if you thought they were insignificant? Why did you have these deviations of protocol -- if you didn't need it for the study, why did you have it in the protocol?

In other words, you have a lot of failures in this study. The study's sloppily done, and poor data is collected. Why did you collect the data just to have sloppy information? It's not scientifically sound.

DR. HERSH: Peter Hersh. Again, we're looking through the large group of protocol deviations. Most of those were indeed intraocular

pressures that were not taken in keratometry. That was missed here and there. These were placed into the protocol.

Initially, I was a clinical investigator at the time. I think certainly this is data that would be beneficial to have, but I think looking at cross-linking as the therapeutic procedure that we're doing, that the kinds of data that we were missing really probably does not influence our assessment, assessment as ophthalmologists, of the clinical safety and efficacy.

DR. FEMAN: You said probably. You have no data to back up what you're saying.

DR. HERSH: Well, we are going to undertake a phase 4 study that's going to be looked prospectively again at three years of data. I'm certain in that study design we may be able to answer some further issues as we continue to follow these kinds of patients.

DR. AWDEH: Dr. Chambers and Eydelman, have we covered everything that you would like to on this discussion topic, or are there topics

remaining on number 1 that you'd like to discuss?

DR. EYDELMAN: I just want to make a comment in light of what was just said at the podium. I just wanted to clarify that for approval, there has to be reasonable assurance of safety and effectiveness prior to approval, and postmarket data is collected as a secondary.

From my perspective, we can move on to question 2.

DR. AWDEH: Okay. We'll pull up question 2. Thank you.

Discussion question 2. For both proposed indications, the studies were to evaluate efficacy three months after treatment as reflected by the protocol-defined primary endpoint. For the progressive keratoconus population, statistical significance was not achieved at month 3. Statistical significance was achieved at month 3 for the corneal ectasia population.

The statistical analysis plan submitted after the last patient visit extended the evaluation of efficacy to month 12, and the

subsequent analysis used a last observation carried forward, LOCF, strategy to impute missing data resulting from patient withdrawal as well as to impute data for sham subjects receiving cornea cross-linking treatment in month 3 or 6.

Please discuss the strengths and weaknesses of the trial design and analysis, including the effect of the following on your evaluation of product efficacy.

Does the use of this technique introduce potential bias to the study? Dr. McLeod?

DR. McLEOD: So I would have to channel Dr. Weiss here with -- if you tried to come up with a design that was sort of a textbook how not to do it, this would probably be it, which is having the ability to have non-random movement from one group to another in the context of selecting patients where you have a high probability of regression to the mean from your base population.

There's just so much noise -- as I indicated before, there's just so much in your initial enrollment that the likelihood that everybody is

going to get a little bit better just randomly is actually pretty high. You divide people into two groups, and then you allow people from one group to move into the other group.

Essentially, what that does is it allows differential regression to the mean between the two groups in a way that can end up producing the sort of outcome we see, which is a very small number of people in the group left behind that actually have better results than the group as a whole and differentiation between the two groups.

You can draw it out, and that's unfortunately the way it works. So unfortunately, the use of the last observation carried forward allows the lower performing groups to cluster together and can produce the results that you have.

I think that the analysis that the FDA did, which looked at the fine results on an intent-to-treat basis really is a lifeline for the study because it did manage to show conservatively that there was a difference between groups. Obviously, it makes it extremely messy. But as

reported with the last observation carried forward, it's just a terrible, terrible mess.

DR. AWDEH: Dr. Sugar?

DR. SUGAR: I would argue that this does induce bias, but it induces bias against the approval of the device rather than in favor of it; that is it would reasonable to assume, and it is reasonable to assume from other studies, that if you follow them longer than 3 months, that is the untreated corneas, it's going to be more steepening over time. Therefore, using the LOCF analysis, this would bias it against efficacy. Nonetheless, there was demonstrated efficacy.

DR. AWDEH: Dr. Evans?

DR. EVANS: Let me first thank the sponsor and the FDA for their thoughtful presentation, as well as the comments from the public. I understand the complexities of these evaluations and proceedings, and I appreciate the efforts to try to understand the data.

There are two elephants in the room, and it's not me looking in the mirror. The first is

the analysis and claim that is based upon data we don't have, at least not directly, a primary endpoint that is not observed for effectively all control patients due to crossover, so nearly a 100 percent imputation. That is massive by imputation standards, and that's the first hurdle that has to be discussed.

Now, last observation carried forward, LOCF, was utilized based on a logical argument whose basis was that there's a progressive nature of this disease. Two comments about LOCF. First of all, perhaps the leading reference these days on missing data imputation was put out a couple years ago by the National Research Council of the National Academies of Science. They generally advise against using LOCF for a number of reasons, that it's valid only under certain assumptions, and that it's biased.

Now, one could argue in this particular case that the bias is in the conservative direction because of the progressive nature of disease. And we'll come back to that point because that's an

important issue.

The other reason they argue against LOCF is that LOCF doesn't propagate the uncertainty associated with imputation. Perhaps in general, patients aren't changing over time, but maybe the variability of their responses is.

If you underestimate variability of the responses, then you'll underestimate. You're going to underestimate p-values. That is not dealt with when you use single imputation methods like LOCF.

The second issue about LOCF, particularly in this case, is that the validity of it and thus the crux of these analyses relies upon the critical assumption that this is progressive disease. So we must understand the natural history for both of these diseases quite well.

Now, there's some evidence that has been discussed about the progressive nature of this disease, and there was a meta-analysis summary that was in the FDA report and figure 1 showing -- for at least one of the diseases, that tends to show some support of this. But my colleague to my left

also gave me pause this morning with some of his comments that there was actually some uncertainty about whether you might call this progressive disease.

Now, this is really important because the entire analysis rests upon this assumption, and without this assumption, everything crumbles.

I don't know if your comment was -- and maybe we could discuss this further with clarification -- whether you meant this is really not progressive disease or whether your comment was more about that Kmax is not really the right measure to measure progression and the status of a patient, which also questions the surrogacy of Kmax, what is the clinical relevance of measuring Kmax.

We come back to this how do you -- is this a measure of how patients feel, function, or survive. And I find it a little bit awkward that some of the measures that were discussed were considered safety measures, although I thought we were trying to improve patient vision, yet we were measuring this

surrogate, which may or may not be -- I'd like to know how good of a surrogate is it for patient function in a sense and clinical relevance of it.

The second elephant in the room is the change in the primary endpoint. There was a fellow who wrote a paper in 2007 called "When and How Can Endpoints Be Changed After Initiation of a Randomized Clinical Trial?" It was in 2007 PLOS Clinical Trials. And the author, he's a suspect author, but he sometimes get lucky. I wrote it.

(Laughter.)

DR. EVANS: Anyway, one of the big issues here is the timeline in the sense that there's no real firewall between the data and the people making decisions about changes and endpoints. As a matter of fact, if I read the timeline correctly from the FDA presentation, prior to the statistical analysis plan being finalized, there were publications about these trials.

So there's a little bit of uncertainty about who knew what and when and whether you start dredging the data, looking for things that work and

things that don't work. And it opens the door for the potential concern for unrecognized multiplicity problems and selective nature of endpoints.

Now, part of the potential defense against that is the motivation, what motivates the change in endpoint. And there were statements from the company and some citations that seemed to indicate that new research had evolved since the original design of those trials that said 12 months is a better measure than 3 months.

I think it would be important to -- I noticed three citations on one of the slides. And I think some of the details in those citations would help us figure out where that motivation came from and whether it's really addressing -- whether it was addressing, saying, listen, you've got to go up 12 months. That's the best place to see these positive effects.

I think those are the key issues. And I'll just go back -- I don't want to go back to the prior issue because I wanted to talk about I think these are the two biggest issues there. But in

terms of the sample size, sample size is relevant in trial design, extremely relevant.

Once the trial is over with in terms of efficacy, it's not that relevant anymore. You have what you have. Whether you've powered it for 90 percent or 2 percent, you have what you have.

Where it does come into play is on the safety side because, as you were illustrating or as this discussion was leading, you need more patients if you're going to be able to reasonably rule out harmful effects with reasonable confidence, particularly ones that are more rare. With 300 patients -- you need 300 patients to rule out things more rare than 1 percent.

Well, obviously, you don't have 300, so it may be 2 percent. The smart folks across the hall could easily back-calculate what percentage of effects you could rule out with reasonable confidence, but it's going to be bigger than 1.

So I'll stop there. Thank you.

DR. AWDEH: Thank you, Dr. Evans. I though the comments were on point with the two issues that

this committee needs to focus on.

Dr. Belin, why don't we go to you first?

DR. BELIN: I have a question. It's actually a question to you after that. The last observed count carried forward, I know were being used in the sham with the assumption that we have a progressive disease. Was it also being used in the arm that was treated?

(Brief pause.)

DR. BELIN: No. It was being used in the eyes that were not treated and not followed, with the assumption that we had a progressive disease. So the theory behind it is we carry it forward. But was it also being used in the eyes that were treated but not followed past a certain point?

DR. ZHUANG: This was used for both arms.

DR. BELIN: Because there I do think it potentially adds a fair amount of bias. First, you remove the epithelium. We don't know the period of the epithelial remolding, but we have flattening effect from removing the epithelium. And if you then carried that data past the period of

epithelial maturation and assuming we're not getting any change, you've already flattened the cornea by removing the epithelium and also the period of maximal thinning by the cross-linking.

The other thing would be is just patient selection If the study was originally a three-month study, and then they had an option to continue, is there a selection bias in the patient's own desire to continue knowing that they can't -- if they wanted the other eye done, they had to continue in the study, most likely. So only those that did well would want to continue. Those that weren't very happy would probably drop out.

So there's a huge selection bias not on the investigators, necessarily, but on the patients' willingness to continue a longer term than they were originally told that they would be in a study.

The other point, I just want to reiterate, I think what you said was -- and I never thought about that -- the last observed carried forward basically stabilizes the data and lowers the noise level.

So when you have minor differences that look like they're statistically significant, you really need to do the same analysis without the last observed carried forward because it may strictly be a fact that you've lowered the noise artificially.

Is that what you were basically saying? Is that correct? I think that's a great point.

DR. AWDEH: So according to Dr. Belin's point, do we know if the last observation carried forward in the treatment arm, have we compared that group versus the observed in the treatment arm? And do we have an idea of how many observations were carried forward in the treatment arm?

DR. CHAMBERS: We'll get it for you in just a moment.

DR. ZHUANG: We have a backup slide.

DR. CHAMBERS: If you want to move on, we'll come back and get it.

DR. AWDEH: So I think that some good points came out of this. I think that, in principle, we believe that the last observation carried forward in the control arm should bias this study in a

conservative bias, with the exception of variance, which is a separate item, which I'm going to get to.

So the exception of variance and measuring at each visit, the observation carried forward in the control arm should bias this study in a conservative manner. Is that correct?

DR. EVANS: Well, I think that's one point to make sure that we agree with, given that I had heard a couple of comments about whether we should really call this progressive disease or not, one from the public I heard as well. I just want to make sure where that assumption really stands. I think that was the rationale for why the LOCF might be the constant.

DR. AWDEH: So let's go back to the inclusion criteria and the definition of progressive disease because I think it's important for your point. Can we pull that slide up, please?

Dr. McLeod?

DR. McLEOD: I was going to say that actually for that reason, I would actually argue

that the last observation carried forward actually can -- depending on how people move from one group to another, can essentially leave controlled individuals who had poor outcomes, who chose to move over to the other group, it leaves their bad data in the control group. And then basically on their end, moves a higher probability of good data because of regression to the mean now into the treatment group.

So on average, essentially you would have people in the treatment group who normalized to mean and you select out poor data into the control group. Does that make sense?

DR. AWDEH: Let's just play it forward so we're all on the same page. If you have a patient with a K of 62 in the control group and at month 3 in the case still at 62. They now convert to the treatment group. Their case carried forward at 62 in the control group.

DR. McLEOD: So let's say we have a race. The runners are actually all the same. You take all their shoes. They've got different size shoes.

Take all their shoes; throw them into a pile. Everybody goes and takes out a pair of shoes.

Now, some are disadvantaged up, some are disadvantaged down. So you now have variance in the pool. You divide people in two groups. Group A, they get to run their race. And as long as group A has a better average time than group B, everybody gets a prize. Group B, they have the chance of leaving and going to group A. They just to get a prize have to be better than the other people in their group.

What will end up happening in group B is all the people with poor times are going to leave group B and go to group A. That's going to leave. And then because you have different point in time that people can leave, essentially every time that people can leave group b, it's the people with the low scores who will leave group B and go to group A. The problem is group B has to keep the bad scores. And what's that going to do is bring that average down and allow the rest of it to go to the mean.

Does that make sense?

DR. AWDEH: The only problem with that is that the people in group B are not making the decision on their own. So let me ask the sponsor to stand up, for someone from the sponsor team to stand up, to please respond.

DR. GIBBONS: Robert Gibbons, professor of statistics, University of Chicago, and I live for the opportunity.

(Laughter.)

DR. GIBBONS: So you raise a wonderful point about regression towards the mean, and it can operate in the way you're describing. But it can't exist in this study for two reasons. And the first is that the people that stayed, who presumably were doing better at 6 months in the control group, looked much worse than the ones at 3 months that switched, who crossed over. So the disease is progressing, as we would expect from the underlying biology.

The second point is, I've spent a career developing generalized, mixed-effect regression

models, which are the antidote for that god-awful last observation carried forward business, that's been so popular in this building for many, many years.

We reanalyzed in appendices 5 and 6 all of these data using generalized, mixed-effect regression models, which do no imputation. They use all of the observed data from each individual, and these are the results of those analyses.

There are lots of numbers on there, but the important thing to see here is that the estimated effect under lots of different model specifications all show the same result.

We're getting overall effects of about 2 and a half diopters for keratoconus, whether we are comparing between subjects, whether we're comparing the subjects who are crossing over those controls versus the other controls, whether it's in the fellow eye or the original eye. And every one of those is statistically significant. There is no imputation.

This model specifically -- every one of

those models that has a slope term for the random effects allows the variance to increase over time. It doesn't have that horrible side effect of last observation carried forward, where the variance at the imputed endpoint goes to zero because there's no longer -- it doesn't go to zero. It no longer is allowed to increase because we know that as time goes by, there's more bifurcation. There's more heterogeneity in the treatment response period.

DR. EVANS: Could you just clarify for a minute? You say you're using only observed data. But if there's no observed data.

DR. GIBBONS: So what we're using is the available data from each subject. So what we're doing is modeling -- there are three different models here. One's a linear model, and it's using all of these baseline data, the 3-month data, and the 6-month data that were available, about 40 percent of the population in the control group and about 80 or 90 percent in the experimental group. And it's using those to build, essentially, the linear response terms over time.

In this slide, these are all log linear, we know that everything in life isn't linear. It tends to taper out as we get further away from time. These were in fact the better fitting models. So these models allow a dampening of the response over time.

So we're using all of those data to overall compare the rates of change through 12 months. And we also have another set of these based on the linear assumption. And then we also have another set of these based on a non-parametric assumption, just treating time as a categorical variable.

Again, you see the same things, the same magnitude in the effect size. It's no longer statistically significant at 12 months because there are only two subjects in the control group. But a 6 months, it's very statistically significant with just having 40 percent. But I like your regression to the mean. It's a beautiful thing.

DR. AWDEH: I think one important comment that came out of that is that in the control arm, we know that there is progression disease. And

you're looking at that in the patients that actually stay in the control arm at month 6 versus the ones that were in at month 3, had a higher Kmax. Is that correct?

DR. GIBBONS: That's correct.

DR. AWDEH: Does that help address your concern?

DR. McLEOD: The thing is, actually from the -- yes.

DR. AWDEH: Yes? Okay. So the next topic here, then, relates --

DR. GIBBONS: Can I just make one final comment on that, which I think is pretty -- and it would be really quick. There are 500 subjects in the safety group; 290 some of these same subjects were in the treated arm, the active treatment arm. We are very much at the 300 number for the 1 percent. Thank you.

DR. AWDEH: So let me clarify that comment, and that is because the fellow eyes and the crossover eyes are included in the pooled safety data. Correct?

DR. GIBBONS: Yes.

DR. AWDEH: The next comment regarding this has to do with the definition of progression and that we actually are selecting patients that do have progressive disease. We'll pull up the inclusion criteria to define progression. I think they're on slide 31.

The comment earlier was regarding a myopic shift in whether this represented true progression or not by Dr. Weiss. Does anybody on the panel have a comment regarding the definition of progression, specifically the comment that was made earlier?

DR. MacRAE: Richard?

DR. AWDEH: Yes?

DR. MacRAE: Just a quick question. Scott MacRae. So can't we separate out the half diopter shifts from the 1 diopter Kmax patients --

DR. AWDEH: That's a good question.

DR. MacRAE: -- and just separate that data out.

DR. AWDEH: Do we know the number of

patients where progression was defined based on meeting bullet point 3 on this slide? Dr. Chambers?

DR. CHAMBERS: It was recorded in the trial. Whether it's available at this time -- we don't have it readily available. I don't know if the sponsor has it readily available. Each of the reasons, whether you met the different things, was recorded.

MS. NELSON: Pamela Nelson, regulatory affairs, Avedro. Yes, Dr. Chambers, we did collect that data. And the vast majority, of course, met the 1 diopter. However, we can go back, and we can look into those individual patient files and provide that information to FDA regarding the myopic shift.

DR. AWDEH: Okay. Dr. Eydelman?

DR. EYDELMAN: I just wanted to bring to the panel's attention that these progressions for keratoconus, to the best of my knowledge, there was no equivalent criteria for ectasia.

DR. AWDEH: Can the sponsor comment on

definition of progression for the ectasia group, please?

DR. HERSH: Peter Hersh. Yes. In the protocol, there was no definition of progression. An assumption was made that the corneal ectatic patients were indeed progressive. There's a lot of literature on corneal ectasia, showing it to be a progressive disease. These are patients who were normal before, and now have a keratoconic appearance. So there was essentially a clinical presumption that these patients had nothing, had developed something, and therefore were inherently progressive.

DR. AWDEH: So the question was, what measure was used to look at progression in the ectasia group?

DR. HERSH: There were not. There were no measurements that were specifically used to define progression in the ectasia group.

DR. AWDEH: Dr. Belin?

DR. BELIN: I'll just comment on that, Peter. I would agree with that totally as long as

you had preoperative data on these patients to make sure that they weren't preexisting ectatic disease that was missed. But I would agree with you. If you have a normal preoperative examination, the presence of post LASIK ectasia is, by definition in itself, progressive.

DR. HERSH: Right. We didn't have the pre-op LASIK topographies, but I agree --

DR. BELIN: So that's the problem.

DR. HERSH: -- that the assumption was that they were not keratoconic.

DR. BELIN: But that's the problem. If you don't have the pre-operative, a lot of these may have been missed, early cones to begin with. But going back to the slide here, and I said earlier, I have a problem with number 4, which is the back optical zone. That's just one parameter. The myopic shift, I agree with Jayne. A half diopter is about the noise -- in a normal population, it's clearly noise level in a keratoconic.

An increase in 1 diopter of regular astigmatism is usually not present in these

patients to begin with and subjective manifest. Any of us who have tried refracting cones know from day to day, you can get a huge variation. So you're really left with the first one, which is increase in 1 diopter in steep K reading.

I want a clarification from the sponsor. Steep keratometry value or simulated K is different than K and Kmax. So the problem I have with that is we have inclusion criteria that define progression that is different than our efficacy variable we're using to define progression.

So minimally, you've got to use Kmax if you're going to use -- I think it's a horrible parameter, but if that's what you're going to use of an efficacy to show that it progresses or it doesn't progress, then you have to show it progresses on your inclusion criteria. You can't have different inclusion criteria to divine a progressive disease, and then come up with a new efficacy variable for progression. It doesn't make sense.

DR. AWDEH: Can the sponsor respond to that

comment?

DR. HERSH: The Kmax outcome was something that was rather new at the time. And for the two years previous in which we had to demonstrate progression, the Scheimpflug imagery and the Kmax was really not available. Rather we depended on manual keratometry, or automated keratometry, or refraction.

We then elected to use Kmax as the primary outcome indicator because we wanted to base it on corneal topography as a quantitative assessment that could be achieved objectively amongst the study centers in an unbiased way.

DR. BELIN: If you had it to determine your efficacy, you had it to determine inclusion criteria. Otherwise, you can't -- if you don't have it for inclusion point, then you have no baseline to determine efficacy. So you clearly had it. So I'm just going to say it again. You can't define an efficacy variable as progression if it's not part of your inclusion criteria.

DR. HERSH: Peter Hersh. Our efficacy was

determined against the baseline Kmax, so we're not doing any comparative analysis with anything that was before entry into the study. So we looked at Kmax, then used that variable as our quantitative indicator of change afterwards.

DR. AWDEH: Are there other comments regarding the measure of progression of disease for keratoconus or for ectasia in this trial? Dr. Feman?

DR. FEMAN: Just to clarify what Dr. Belin was pointing out earlier, for the patients that you're describing as having corneal ectasia after previous LASIK surgery, you're only using one measurement of ectasia to qualify for entry in the study. So you don't know if the ectasia is changing from day to day.

So there are patients that have a single ectatic point. So it's not a measure that they're having progression of their ectasia, the patients that are found at one place in time to have ectasia. They didn't have it perhaps before they had the refractive surgery, but they were ectatic

at the time that you were seeing them.

DR. HERSH: That's correct. The entry criteria that they were ectatic at the time that we saw them. They had to meet the study criteria, and their topographies were reviewed in an independent study center. But we did not have to show explicit progression as we did with keratoconics. It was somewhat implicit in their problem that most of them did not have keratoconus beforehand, and they developed it afterwards. And they were thought to be inherently progressive, and in then the nature of their disease.

DR. AWDEH: Thank you to the sponsor. I'd like to put up one more slide here before we take a break. Can you put up the timeline slide, please? There was a comment made regarding the change of primary endpoint and whether there's a firewall between the data and the people making the decision.

Dr. Evans, you can take a look at the timeline that's in front of you and share your thoughts with the group, please.

DR. EVANS: Well, my point was that the analysis plans, which is the second line from the bottom. And when they were finalized, what I had seen was that there was this paper published above it that was submitted and accepted and published prior to the SAPs being finalized, which means somebody was in the data, and knows what's going on, and could be some questions about, well, those were the other folks and not necessarily this team.

But what that means is that if people are looking at the data, there are opportunities to be very selective about which endpoints you choose. So there are multiplicity issues going on and endpoint selection issues going on.

So it's very hard to figure out, with the way this is played out, whether there are unrecognized either selection or multiplicity issues to be concerned about because other -- there may have been other -- since there was one change of endpoint, they may have considered several, and are we just picking an endpoint because 3 months wasn't significant for one of the diseases, so

let's look for something else.

You have to have a way of wrapping your head around a multiplicity context to understand that sort of thing. And the way it played out, there wasn't clean control of that, and so there's that issue to be aware of.

DR. AWDEH: Dr. Weiss?

DR. WEISS: Just a quick question on that. Was the decision to change from 3 months made at the same time for the progressive keratoconus and the corneal ectasia or was it made at different times? Because I would assume you should have made it at the same time.

DR. MULLER: David Muller. Same time.

DR. AWDEH: Dr. Eydelman?

DR. EYDELMAN: I was just wondering if Dr. Hersh can comment on how many papers were published prior to 2011. I know this slide alludes only to one such publications. I believe there were more.

DR. HERSH: There was one other publication that our group did prior to this publication on our

own patients in our single center, and that dealt with corneal haze after cross-linking.

DR. AWDEH: I'd like to ask Dr. Eydelman and Dr. Chambers if we've discussed this topic sufficiently or are there remaining questions that the agency would like the panel to discuss?

DR. EYDELMAN: Does the chair mean just sub-bullet A or the whole question? Because there were --

DR. AWDEH: I think we've discussed everything with the exception of number 4.

DR. EYDELMAN: Correct.

DR. AWDEH: So let me pull the question back up, please. Regarding bullet point number 4, which is stability of corneal response to treatment, does the panel feel that this trial has demonstrated stability of corneal response to treatment based on the data that was presented today? Dr. Sugar?

DR. SUGAR: It isn't stable. It's changing over the 12-month period. That's why they went from the 3-month to the 12-month endpoint. So the answer is no. The phase 4 will maybe give that to

us. There's a paper published this month in the German literature by Spruill and the people from Dresden that showed changes up to 10 years. And they had just 40 patients, and they went from a mean of 62 to a mean of 57 diopters maximum K.

I suspect that the changes are long-term, and I don't know that approving this would require stability but rather progressive improvement.

DR. AWDEH: So as long as the change is in the correct direction, stability is not necessary from your standpoint.

DR. SUGAR: That's correct.

DR. AWDEH: Does anybody disagree with that comment? Dr. Eydelman?

DR. EYDELMAN: I just wanted to once again clarify that there is no phase 4 for a preclinical study. We're talking about preclinical study that demonstrates reasonable assurance of safety and effectiveness. If the bar is met, the product gets on the market. And then the separate question is if post-approval is needed. I just wanted to clarify one more time.

DR. SUGAR: I understand.

DR. AWDEH: Any remaining comments regarding bullet 4 on this discussion question?

(No response.)

DR. AWDEH: Okay. Let's take a 10-minute break. At this point, I'll remind everybody not to discuss these proceedings during the break, and we'll resume in 10 minutes time.

(Whereupon, a recess was taken.)

DR. AWDEH: If everyone could take their seats, please. We're going to move forward. I would like to start. Thank all of you.

I'd like to start with the agency. There's a clarification on a slide. So please go ahead.

DR. MOKHTARZADEH: Yes. This is Dr. Maryam Mokhtarzadeh. Just with regard -- and I apologize for the busy slide -- with regard to the question about publications related to study results, there are a number that have come to our attention that were published using the clinicaltrials.gov number for these trials.

So based on those numbers, there are quite a

few, if you look at the date of publication, that might have been before the SAP. So just in light of this information that's come to our attention, I wanted to invite the sponsor to clarify the last comment they made. Again, I'm sure you have more information.

I believe Dr. Hersh was an author on all of these papers, and therefore that's who I think the clarification should come from the sponsor. Thank you.

DR. HERSH: Right. These are all single center analyses that we did in our patients from the clinical trial. To answer the last question, there was one paper that was before the paper that we had addressed before, which dealt with the natural history of corneal haze after cross-linking. The rest of these are sub-analyses of different outcomes of collagen cross-linking.

Again, this is something that we did in our own study site to look at the results from the patients that we had treated with cross-linking at the time.

DR. EYDELMAN: Dr. Eydelman. So just to clarify Maryam's question, I guess her was specifically how many papers were submitted with a difference of analysis over the study prior to the SAP.

DR. HERSH: The SAP date was what again, if I may ask?

DR. MOKHTARZADEH: December 2011.

DR. EYDELMAN: December of 2011 it was --

DR. HERSH: So then there were the one, two, three, four, five papers that you see here, one on corneal thickness changes, one on corneal topography changes, and in vivo biomechanical changes. And that was on our group of patients.

DR. EYDELMAN: Thank you.

DR. HERSH: The only one that dealt with actual clinical results is the one that we had addressed before, the second one up there.

DR. AWDEH: Thank you.

Let's move forward to the third discussion topic. If you could pull the slide up, please.

In these studies, at the time of treatment

there were the following number of pediatric patients enrolled, stratified by less than 21 years for CDRH and less than or equal to 16 years for CDER. The columns are slightly off-center on the slide that's in front of you, but the slide is up for your viewing.

For the proposed indication for progressive keratoconus, please discuss: What is the minimum age supported by the data, and what is the applicability of extrapolation from adult data to the pediatric population?

Let's start with the first question. What is the minimum age supported by the data presented today? If you could go to slide 69, please. Thank you, Moon.

So the definition of the pediatric patient population is at the top of the slide for the panel. These are the number of patients that were treated in the pediatric population.

Dr. Eydelman?

DR. EYDELMAN: I just wanted to provide further clarifications. While we provided

definitions for drug and devices, we're not asking you to make a decision upon one or the other of the definitions. We actually want an age that you believe is appropriate. Thank you.

DR. AWDEH: So what age does -- yes, Dr. Leguire?

DR. LEGUIRE: Larry Leguire. I'll start it off saying there's nothing that can be said about this data in terms of determining a minimum age for the procedure.

DR. AWDEH: Does anybody have a different opinion from Dr. Leguire?

(No response.)

DR. AWDEH: Okay. What is the minimum age that this panel feels comfortable with corneal cross-linking?

(No response.)

DR. AWDEH: Let me ask that in a different way.

(Laughter.)

DR. MacRAE: If you're asking if it's based on this data, I think your answer -- based on what

I've heard and what I've read in the literature --

(Technical difficulty with audio.)

DR. AWDEH: Sorry. Your mike cut out right when you said the age. He said age 10 to 12 is --

DR. AWDEH: Yes, Dr. Weiss, do you have a comment?

DR. WEISS: So this is where that elephant starts moving around again.

(Laughter.)

(Technical difficulty with audio.)

DR. WEISS: But in any case, so we've got the literature and we've got the study. The study didn't look at anyone age 10 to 12, so we can't approve it for someone age 10 to 12 since no one was in the study.

So the lowest we can go is the lowest the sponsor has given us, if that's what you chose to do. But then we're still back to on the basis of this study versus on the basis of the literature, I guess.

DR. MacRAE: So is the pediatric group equivalent to the adult group in terms of the

clinical course and results? That's the basic question for the sponsor.

DR. AWDEH: Dr. Belin?

DR. BELIN: Yes. I think we just need a clarification. The second way you reworded the question was not pertaining to the study. You asked us just what we view as the minimal age. But that's different than asking us what we think the study -- and also, this is another cart before the horse.

To ask us what we think the minimal age this study supports suggests that we think the study supports approval. So you're asking us to sub-select a limit on something that we may not think supports anything yet. So it's a little bit --

DR. AWDEH: Well, at the end of this we will ask you whether the study --

DR. BELIN: But the first question. Do you just want a general panel consensus of what we feel?

DR. AWDEH: Yes. Let's start with that.

DR. BELIN: Versus what the study supports?

DR. AWDEH: Well, hold on. There are three different things going on. Number one is, what does the study support? What does the data here support? And to that, I have got zero answers, and I actually got an answer that the data does not support this population.

Does anyone have a different opinion than that?

DR. McLEOD: Stephen McLeod. I guess in principle, if you were to say should the study support patients between the ages of 30 to 32, and we looked at that and said, well, there are only three patients in 30 to 32; are we going to approve it, I think that really what you're left with is what did the study include?

So I think that it's reasonable to use the numbers the study included, recognizing if you parse it down to any two years of age, you're going to have small numbers.

DR. AWDEH: Let me challenge you on that. So using the data the study includes, how

comfortable are you with the applicability of extrapolating the adult data to the pediatric population?

DR. McLEOD: Different question. If you go outside of the study parameters, I think that it is -- now again, you have to look at the experience outside of what's presented. And so there is no question that pediatric corneas are different. They have different biomechanics, and they have different disease progression.

So is it fair to extrapolate the data to pediatrics? I would say perhaps not, and we should go with the data we have on hand in principle.

DR. AWDEH: Let's go back to slide 68, then, please. This slide shows the age of each patient, and the lowest age we have is 14 years old, Dr. McLeod and to the rest of the group. And here are the patients receiving corneal cross-linking between the ages of 14 and 21.

DR. McLEOD: I'll stand with my principle that if they're included in the study, that's what we approve -- we consider approving.

DR. SUGAR: Do we know how many of those crossed over from the sham group?

DR. AWDEH: We'll look at that and get back. Sorry. Go ahead.

DR. CHAMBERS: This is Wiley Chambers. If you go back to the slide you had before, I had each of the different groups. That's how many total eyes there are and how many sham eyes were treated, as well as the primary.

So while people are looking at it, let me just make the comment. There are two different issues, and they're what's listed within the questions here. One is what the data supports if you were trying to make an efficacy question.

The other is, can you extrapolate from adults? And if so, you may not feel comfortable extrapolating to all age groups. You may not feel like extrapolating to any of the age groups 21 or below. But we're asking you, is there an age group which you think the adult data can be extrapolated from an efficacy perspective?

Safety we don't extrapolate down. From a

safety perspective, the lowest we would go is the minimum age that we thought there were enough patients. But efficacy, we can potentially extrapolate that, and if you think the disease is the same. But what age, if any?

DR. McLEOD: Can I answer that? Stephen McLeod. Again, it's not as if you're falling off a cliff. So I think that once you have data that is young adult data that will -- there's going to be, one would imagine, a linear gradient into a younger population.

So it becomes completely arbitrary, but it stands to reason that you can indeed allow yourself some extrapolation. And unfortunately, it's some degree of hand-waving. And if you're going to choose a number, then the number that is presented in the study seems reasonable to me.

DR. AWDEH: Dr. Belin?

DR. BELIN: Put the slide up that had the distribution by age. Yes, right there. I'll give two completely different answers. The problem with what you just said would be let's say we had a

group from 14 to 21, and 14 to 70 was the inclusion criteria for the study. And we had one patient in the 14 group and no one else till 25 years of age. You would not probably feel comfortable saying 14 to 21. So really, you do need to look at the numbers. I don't think the numbers are adequate in this study.

But then I'll agree completely with Scott. I think if you ask it outside the study, I think the international data is adequate to suggest efficacy in a pediatric group, and that's clearly the group that has the greatest potential benefit.

I think the real goal here is not stabilizing disease once we got advanced disease, which is really what this study is, but trying to identify these early cones and stabilizing before they get loss with respect to corrected vision. And to do that, you've got to do it early. That's not study-related, though.

DR. AWDEH: Agreed. Can you pull up slide number 70, please? Dr. Belin, I'd like you to take a look at this slide. This looks at ages 14 to 16

and 14 to 21, and looks at the efficacy. Is this consistent with what you would expect from the international data and data outside of this trial?

DR. BELIN: The problem is when you look at it, month 3 you show a minus 2.6. It then kind of regresses at month 6. And then at month -- it's just the numbers are so small, it's just really -- again, I'm very comfortable in pediatric patients. But again, if you ask me, does this study give enough data based on just the study, I'm not comfortable with the study.

DR. AWDEH: Dr. Eydelman?

DR. EYDELMAN: Once again, I realize we all have seen a lot of literature for U.S. I just want to bring back the panel's attention to the fact that the product before the panel that you're considering approval is a specific device and specific drug combination for which I believe the sponsor has not provided literature demonstrating this particular point. So again, the decision hopefully is made based on objective data that is present.

DR. AWDEH: Dr. Owsley?

(Brief pause.)

DR. OWSLEY: Cynthia Owsley. I thank Dr. Eydelman for that comment because it's directly along the lines I've been thinking about this, given the way the question is written. It's in these studies and it's about this specific device and product combination.

In answer to A, given the data, what is the minimum age supported by the data, I agree with Dr. Leguire. We can't really answer that question, and applicability of extrapolation from adult data, based on these studies, we don't have enough information.

Now, there's the literature. But the sponsor really didn't do a comprehensive review of the literature for us or even allude to it very much. So I think my responses to this are very straightforward.

DR. AWDEH: Cynthia, can you just state your responses, please?

DR. OWSLEY: In answer to A, what is the

minimum age supported by the data, it cannot be determined from these studies, the data from these studies. And in terms of applicability of extrapolation from adult data, I would say the adult data are inadequate for extrapolating to pediatric applicability.

DR. AWDEH: It seems that, in summary, we have two different schools of thought. One goes along with what Cynthia stated regarding both topics. The second is that the minimum age supported by the data is actually the minimum age that was tried in this trial, which is 14 years.

Are there any other comments on this topic?

(No response.)

DR. AWDEH: Let's move on to the next discussion topic. Let me just making a clarifying point on number 3, that the second school of thought was that within this trial, the applicability of extrapolation of adult data is that there's not enough data to make the decision. However, there is a thought that there's data outside of this trial to help make that decision.

So question number 4. Please discuss your interpretation of endothelial cell count findings. And we will pull up the endothelial cell count tables.

Dr. Sugar?

DR. SUGAR: The data appear to show great variability in measurements, but do not show evidence of toxicity based on this pooled data. We did not get an answer to the less-than-400-micron patients, and pending that data, I would say that there's no evidence of endothelial toxicity to the procedure, as defined in the protocol.

DR. AWDEH: Thank you. Are there other comments regarding endothelial cell counts?

DR. EVANS: It just might be useful, instead of looking at summary statistics at different months, to perhaps look at the proportion of patients that have changes that are "concerning." And I think that may be more informative in a sense, to try to evaluate safety in this context.

DR. AWDEH: I want to expand on Dr. Sugar's comment first, which is, can you comment on the

performing an endothelial cell count measurement in a patient that has a steep cornea and the variability of obtaining that measurement in this patient population?

DR. SUGAR: There is data suggesting variability in cell size and shape with the steepness of the cone. But the literature is actually all over the place, nothing that is consistent. I think the best stuff is the stuff from Australia.

Given that, and given that at different points on the cone, if you measure cells, you're going to get different sizes and shapes, I would agree with Dr. Hersh that the measurements can be very difficult to repeat unless you go into the same spot, and there's nobody going to the same spot.

DR. AWDEH: Thank you. Are there other comments regarding the performance of endothelial cell count in this patient population and/or the toxicity?

DR. MacRAE: I'd agree with Dr. Sugar in

terms of the endothelial cell count. The data looks reasonable. The one criteria that one could look at is if there's, let's say, more than a 25 or 35 percent cell loss individually, which kind of speaks to your point. If you see that, then that's a red flag. And it would be helpful to see that.

If you see it, the other piece of this is if it's consistent, so that if there's a drop of 25 to 30 percent on an isolated basis and it's persistent, that's a concern.

DR. AWDEH: Dr. Chambers?

DR. MacRAE: We didn't see any data. They didn't present data that showed that. But it's a good way to analyze it.

DR. EVANS: I think the point is that when you do summary statistics like this, you might mask concerning changes among a small subgroup of patients. But because they're sort of clumped in with everybody else, it gets diluted here. So sometimes it's worthwhile to define something you consider concerning and then look and see what you're getting there.

DR. AWDEH: Thank you.

Dr. Chambers?

DR. CHAMBERS: Can I ask Avedro to put up their slide, the CC-84? I just want to ask if this is what you're talking about.

DR. AWDEH: Dr. Evans?

DR. CHAMBERS: Or were you talking about something different than this? Oh, I'm sorry.

DR. AWDEH: Dr. Evans?

DR. CHAMBERS: If that's the case, then that's fine. We can move on.

DR. AWDEH: Is this what was being asked for or were you saying on a case-by-case basis to determine whether there was a change that was greater than 25 percent in endothelial cell counts? And does this satisfy you?

DR. EVANS: No. This is it, I think. Yes. I'd defer to my colleagues on what sort of percent changes are to worry about.

DR. MacRAE: Yes. I think in dealing with -- I've talked with Rudy Nuijts from Holland, who's done a lot of work on this endothelial issue

in terms of phakic IOLs recently, and it's difficult because you do have these outliers, and for the exact same reason that Dr. Sugar pointed out, that you're sampling from different places, so you get more variability. And you're going to get some outliers.

But if you have a cell loss of more than 25 to 30 percent and it's persistent, or a cell drop, to us that's a red flag. And if the cell count's dropped below usually -- if that happens and the cell count's dropped below 2,000, that's another red flag. So that would be my advice. And I'll leave it at that.

DR. AWDEH: Does this slide adequately --

DR. MacRAE: I'd like to see the individual -- I don't think we can do that today, but I'd like to see the individual cases where the cells drop. Sometimes it's just a variant in terms of sampling.

DR. AWDEH: All right. So I think that regarding this topic, the panel feels that there is some variability in endothelial cell count

findings, but it is secondary to the actual measurement in this patient population; and secondarily, that there's not a concern for toxicity.

There are two items that are pending. One is what Dr. MacRae just requested, which is to look on a case-by-case basis at an individual that had a drop greater than 20 or 25 percent of the cell count or below a threshold count of 2,000.

The second thing that was requested was by Dr. Huang, which was in patients that had a corneal thickness of less than 400, to look at that patient subset to determine whether there was toxicity in the endothelial cells.

DR. MacRAE: I'd just add that with that 25 to 30 percent with a cell count drop below 2,000, those two together, because there are patients that do have low cell counts that start the study, and if they drop 10 percent or whatever, that may not be relevant.

DR. AWDEH: Let's move on to the next discussion question, which is number 5.

The studies were conducted on a different device, the IROC UV-X, than the one proposed to be marketed, the KXL System. Differences include but are not limited to the following: Illumination diameter; UV focal length.

In light of the differences and lack of any data collected using the KXL System, please discuss the adequacy of the current data set to assess safety and efficacy of the KXL System.

So we're going to pull up a summary slide here for the group, and I will ask Mr. Pfleger to start.

MR. PFLEGER: Yes. Just from an industry standpoint, it is not at all unusual to start out with an instrument that is -- if you would, it's a beta version. And then as you're getting closer to developing and having a product that you want to go to the market, you're going to do the things enhancing its usability from a patient standpoint and a physician standpoint. And it's certainly going to look a lot better than the original equipment that you use in these trials.

So from that standpoint, I would ask that you don't focus in on those things that are perhaps not with the business end, which is, did you deliver the same thing to the patient.

DR. AWDEH: Dr. Eydelman?

DR. EYDELMAN: While I agree that it is often that the sponsor modifies the device during the clinical trial, we still assess adequacy of the final model for marketing in light of the changes and whether we believe the clinical data might be needed to assess those data. So hence the question.

MR. PFLEGER: And I absolutely agree. Anything that could have an impact on the clinical in the device.

DR. EYDELMAN: Correct.

DR. AWDEH: Let's start with illumination diameter. Yes, Mr. Leguire?

DR. LEGUIRE: Larry Leguire. Just overall, they're really clinically equivalent. My God, are you going to put difference in color up there, too? At some point you've got to look at the variables

that affect the patient, and when you do, they really are equivalent. They look equivalent to me, and looking at every variable, there's not anything appreciably different here.

DR. AWDEH: Thank you.

Let's start now with specifically the illumination diameter. The smallest diameter that was used in the trial -- we can pull the data up -- there were three sizes, 7.5, 9.5, 11.5. The smallest that was used was the 9.5 millimeter aperture, and the current device is a 9.0 millimeter aperture.

Does the panel view these two as equivalent? Dr. Weiss?

DR. WEISS: I don't view them as equivalent. I wish there was some data on the 7.5 because that would have allowed me to see what the data was with a smaller aperture, but we don't have it. So we only have something that's slightly larger and a 9.0. We don't know what the 9.0 will yield.

We can imagine. We can theorize. We can assume. But this meeting is not about assumptions.

It's about looking at the data. We don't have the data.

DR. AWDEH: Dr. Belin?

DR. BELIN: I would suggest that the few patients, the few that were treated with the 11.5, should be taken out of analysis. That's clearly a markedly different treatment parameter. 11.5 squared is probably about 130 versus 81, so the treatment zone is over one and a half times as large.

9.5 and 9 you would not think would be that much different. The red herring or the little area of concern is that fact that it was noted that using the UV-X, patient fixation was poorer.

So that 9.5 probably treated a larger area than 9.5, while if you have excellent fixation at 9.0, you're treating 9.0. So what I don't know is if you're really treating 9.5 or 10.5, and that's a very big difference. That's like another 30 percent treatment zone. And that could affect efficacy.

DR. AWDEH: Thank you.

Dr. McLeod?

DR. McLEOD: Yes. Just in theory as well, so the difference is not just the spot size, but it's whether it's fixed or not. So if I understood the presentation correctly, it would then imply that you have the potential for a fairly sharp transition from treated to untreated zones with the KXL system, which in theory, then, establishes a situation where you have a fairly rigid plate that abuts against a more flexible area.

So generally, where you're going to get stresses becomes that transition zone. So I think it's probably trivial, but there is actually in theory not only the effective size but also the biomechanical effect of a transition, a sharp transition, from a fixed to a more flexible area.

DR. AWDEH: Dr. Feman?

DR. FEMAN: Well, we're just looking at this with anecdotal data regarding the difference in illumination diameter and saying how people responded and whether or not they were holding still or moving at the time. So I think we really

don't have any data for the KXL system.

DR. AWDEH: Let me go back to Dr. Belin's comment. Regarding fixation, this newer model of the device includes aiming lasers and a joystick so that the operator has the ability to, during the case, make sure that the treatment zone is lined up with the cornea. Does that address your concern?

DR. BELIN: No. It's actually the opposite. It may be a much better device than the original. I'm not saying one way or the other. What I'm saying is that can we say they're equivalent? Because clearly, the 11.5 millimeter zone is not.

But with the 9.5, with patient movement -- and we all remember back in the original days of excimer when we didn't have pupil fixation -- you were treating a much larger zone. So what I don't know is if the 9.5 is actually treating out to 10.5. And what would also be a variable which I don't know is the epithelial removal zone.

If the epithelial removal zone was variable -- I assume the sponsor can answer

that -- but even if the epithelial removal was only to 9 millimeters, there's some question about it beyond treatment. So they may be somewhat equivalent, but there are definitely differences between them.

DR. AWDEH: So just to go down your line of thought, how important is the treatment of the peripheral cornea versus central cornea in your mind?

DR. BELIN: Keratoconus is a disease of the collagen, and the collagen goes limbus to limbus. I'm more concerned with the very small zone, particularly with off-axis cone. So I think, and again, I don't have any data, but in theory, the larger the zone, potentially the more efficacious it would be. You would like to stabilize the entire cornea if you could biomechanically in theory.

DR. AWDEH: Dr. Eydelman?

DR. EYDELMAN: In light of Dr. Belin's comment, I was wondering if we can project slide 18. Yes. So while there were very few subjects,

10 out of 102, it's about 10 percent of the keratoconus patients were treated with the large zone. So it takes us down to the sample of 92.

DR. AWDEH: So back to Dr. Belin. The comment, you'd rather have a larger zone, the sponsor has provided a comment earlier that the balance is that the larger the zone, the higher the risk of other complications or other things happening, specifically toxicity of the limbal stem cells.

DR. BELIN: That's way out. And I don't want to quote it and I just thought it was recent, and I'm going to actually probably defer -- because they're keeping up with the literature much more than I am. I believe there was a recent paper suggesting a lack of limbal stem cell damage from -- is that correct? Yes, they're all nodding, so I am pretty up with my literature, then.

So that's probably not a major concern, so to me, a larger zone is potentially more efficacious. Again, we don't have data because it wasn't analyzed.

DR. AWDEH: Dr. MacRae?

DR. MacRAE: Yes. I just want to throw in that the de-epithelialization zone is the same for both studies. Is that correct? So unless the sponsor can guarantee that the patient's not going to move 250 microns, which is the difference that we're talking about in terms of the actual lateral XY movement, I'd be surprised if the system doesn't allow the patient to move 250 microns during the treatment.

So I think that the two zone sizes are probably quite similar, although as there is movement, that peripheral zone probably gets a little less dosage. But I would be very surprised if the patient's not moving 500 microns intermittently during the procedure.

DR. AWDEH: So back to the question, then. Based on what you just said, what is your level of comfort between the equivalence of a 9.5 zone and a 9.0?

DR. MacRAE: I think that they're very equivalent, especially if the de-epithelialization

zone is the same.

DR. AWDEH: All right. So I think that there are two schools of thought on this topic. I think that one is that these are equivalent, given that the patient fixation is there. And the other is that the peripheral cornea may be more important and that you'd prefer to have a larger zone.

Dr. Belin?

DR. BELIN: I don't have a problem. But are we all in agreement that the 11.0 data should really be taken out of the analysis? That's really the only point I was trying to make earlier.

DR. AWDEH: I saw one head nod. Two, three, four, five, six. Okay, seven. All right. So fine. I think that's the other comment, is that the 11.0 millimeter data should be taken out when looking at this.

Any other comments on this discussion topic?

(No response.)

DR. AWDEH: Let's move on to topic number 5, then -- sorry, topic number 6. Oh, sorry. Go back to number 5 for one second. The focal alignment

slide, let me show -- so still on question 5, one of the purported advantages of this new system is this UV focal alignment, which is demonstrated in the graphic shown above.

Is it the opinion of the panel that, A, this actually enables the operator to maintain the treatment zone on top of the cornea during the 30 minutes of treatment? Dr. Weiss?

DR. WEISS: Again, we have no data. It's theoretic.

DR. AWDEH: Dr. MacRae?

DR. MacRAE: I think that the data that we have is different than the system that they're proposing. And I agree with Dr. Weiss that we don't have any data in terms of that. But the parameters of the system are very similar to the parameters for the Dresden protocol. They're essentially identical except for the different optical zone.

DR. AWDEH: Thank you.

Discussion number 6: Please discuss your recommendations regarding the need for analysis, if

any, on the additional data that have been collected during the clinical trials to adequately characterize the safety and efficacy profile of this combination product.

DR. LEGUIRE: Larry Leguire. Can you be more specific about what data you're referring to?

DR. AWDEH: The question is open-ended on purpose. Is there other data that you are interested in seeing?

DR. LEGUIRE: Larry Leguire again. Only if there is actually data. And we could guess all day about what other data there might be. I think it would be a lot easier to tell us what data there is.

DR. AWDEH: Dr. Eydelman?

DR. EYDELMAN: As Maryam provided in her comments before this question, we would like for the panel to refer to slide 37, if we can project that.

DR. AWDEH: Dr. Owsley?

DR. OWSLEY: Yes. It's concerning to me that so far we really don't have any patient-

reported outcome data, not just patient satisfaction but the kinds of domains that are asked about on the RSVP. We did see this slide, which was difficult to interpret because it was basically means, and I'm not even sure who it represented in terms of the studies.

So I would suggest a thorough analysis of that data addressing some of the questions that I mentioned earlier, which should be in the record. And also, there was another questionnaire given at the same time frames. I believe it was called the subjective complaint questionnaire. And there was nothing mentioned about this at all, and that could be potentially revealing about what patients think about this intervention.

DR. AWDEH: Thank you.

Dr. Belin?

DR. BELIN: Since the primary subjective machine they used was a Pentacam and we're trying to document stability another improvement, minimally looking at the best sphere from both the posterior surface and then also on the anterior

service, it would be a more global parameter than just Kmax.

While cross-linking thins the cornea, it eventually comes back, and looking at a PACK measured progression. These are all parameters that are readily available and can be retrospectively gone back and looked at off the Pentacam data.

DR. AWDEH: So there's a request for additional parameters from the Pentacam to be analyzed in this data set.

Is there other data that this group would like to see? Dr. Sugar?

DR. SUGAR: We already the substratification of those that had the hypotonic riboflavin.

DR. AWDEH: Yes. So that is already marked in the record.

Are there any other data points or data sets that this group would like to see? Dr. Weiss?

DR. WEISS: I'm just going to reiterate Dr. Belin's initial question on seeing what happened to the control group of the patients who

were cross-linked for keratoconus in terms of the fellow eye, looking at individual patients who opted to have treatment and those who opted not to have treatment in terms of what the results were in the initial eye as a subgroup.

I personally would like to see a breakdown of the definition of the progressive keratoconus in terms of number of patients who were .5 diopters or less as far as those patients being taken out of the group to see how everyone else did because I don't think that's progressive keratoconus.

DR. AWDEH: Thank you.

Dr. MacRae?

DR. MacRAE: If that's the sole criteria. Right?

DR. WEISS: Yes. Yes. Exactly. If it's the sole criteria.

DR. AWDEH: Are there other requests from Dr. Eydelman or Dr. Chambers regarding this discussion topic?

DR. EYDELMAN: No. But before we proceed to the next question, I was just wondering if we can

take a step back for one second to the previous question.

DR. AWDEH: Sure.

DR. EYDELMAN: In light of Dr. MacRae's comments, my staff was just checking. It does not appear that the protocol was -- it appears that the whole cornea was the -- I can't say it -- epithelium was removed from all of 9.5 millimeters. So I would like the sponsor to clarify if we're not correct in this assumption.

DR. HERSH: I believe that we used a 9.0 millimeter optical zone marker to delineate the area of epithelial removal and stayed within that 9 millimeter optical zone. One of the concerns was going out too far for fear of damaging limbal stem cells. So I believe we were instructed to do 9.0 millimeters.

DR. EYDELMAN: And if you could be kind enough to point where in the protocol or instructions that was written because we couldn't locate that.

DR. HERSH: We'll have to check that for

you. This is just my recollection as a clinical investigator.

DR. EYDELMAN: So Dr. MacRae, if the epithelium removal is not the same, would you have a different answer?

DR. MacRAE: I don't have enough information. My intuition is that it's probably the same. I don't see ectasia very commonly out at 9.5 millimeters. The one concern I would have over a long period of time, and hopefully this is much longer, that these patients, based on the Dresden data of 10 years, that this is a sustained process.

But the one concern is whether these patients have a pellucid marginal type of problem 20 years from now. But my intuition is that by then we'll have even better solutions for this type of problem. But at this point in time, this seems to be a reasonable option. Either 9 or 9.5 are pretty similar. That's my intuition.

DR. AWDEH: Dr. Huang, do you have a comment or question on this topic?

DR. HUANG: Yes. I echo my sentiment

similar to Dr. MacRae in the sense that when we create an epithelial defect, we are not really try to just limited treatment. We are treating facilitated delivery of the riboflavin.

So the standard treatment, whether it's 8 millimeter, 7.5 millimeter, the riboflavin, just like we use in the fluorescing staining on the cornea, it's going to diffuse out. So if you use 9 millimeter, it's going to reach the peripheral cornea, maybe even limbus. You use 9.5, it's still going to be the same.

So essentially, we are try to saturate the riboflavin into the corneal stroma throughout so epithelial defect facilitated delivery. So the size probably doesn't matter that much. Yes.

Because some of the protocols, as you know, is epithelium -- and then try to use the benzalkonium chloride to enhance the perfusion, and it still claim to achieve some effects.

DR. EYDELMAN: Thank you. Please proceed.

DR. AWDEH: Thank you.

Let's move on to question number 7: Please

discuss any potential safety issues. Are there any safety issues that are concerning to the panel? Dr. Leguire?

DR. LEGUIRE: Larry Leguire. One of my concerns would be in the pediatric population, that they develop keratoconus and then stabilize. There would be a tendency to see the initial development of it and then want to treat these kids before they really stabilize.

So I think one safety issue would be treatment of unnecessary cases in the younger population unless adequate safeguards are established in terms of progression.

DR. AWDEH: Thank you. Any other comments regarding safety? I'm trying to look for a slide now. I do want to point out we've talked about safety in question number 1. And I want to be clear with the panel that in terms of a safety analysis, there are actually 290 patients that were included in the safety analysis. It included people that were randomized as well as control eyes that crossed over and fellow eyes that crossed

over.

So there are 290 patients in the safety analysis. Is there a slide number that we can pull up for the group to look at?

DR. MacRAE: Richard?

DR. AWDEH: Yes?

DR. MacRAE: How much follow-up? The 12-month follow-up?

DR. AWDEH: I believe so. Let's pull the slide up first.

DR. HERSH: Peter Hersh speaking. The analysis comparing treatment to control comprised some 384 eyes. And when we looked at all eyes, all eyes that were treated with cross-linking, there were 512 eyes in the safety database. So the total number of eyes treated, 512 eyes, were all followed over the 12-month period for safety.

DR. AWDEH: All right. So let's pull up slide 72 from the FDA slides, please. So these are the common adverse events in slide 72, continued to ocular adverse events greater than 5 percent.

Dr. Weiss?

DR. WEISS: I have some confusion personally on the 290 versus the numbers we saw from the FDA. So was this additional -- does this add up to 290?

DR. AWDEH: Dr. Chambers?

DR. CHAMBERS: Wiley Chambers. The difference between the two slides is one is just the first three months. The other is any time, any eye. So this is the group that you're referring to. This is eyes. This is not patients.

DR. HERSH: Peter Hersh speaking. If you go back to the last slide, so in the pooled keratoconus group there are 219 plus 74, which is 283, if I do the math quickly; in the pooled ectasia, 162 plus 57.

It's the same numbers when we show our database here -- 293 keratoconus eyes were treated and followed for safety, and 219 ectasia eyes had cross-linking and were followed for safety. So over 500 eyes were treated with cross-linking and followed for the safety database.

DR. AWDEH: Given those numbers, since it sounds like there are no objections from this panel

regarding safety -- Dr. Weiss?

DR. WEISS: I suggest listening to what was said in the public portion. We do have almost 300 eyes with progressive keratoconus, and there was no safety issues that I had concern about. But we're not meeting the same sort of numbers for the ectasia eyes, so I don't know that we're able to assess safety in the same manner because the number of eyes don't meet the same amount.

DR. AWDEH: Does anybody else on the panel share the same concern as Dr. Weiss? Dr. Sugar?

DR. SUGAR: No.

DR. AWDEH: Dr. McLeod?

DR. McLEOD: A different issue, if I may.

DR. AWDEH: Say again?

DR. McLEOD: A different issue, if I may, a different safety concern -- well, less of a concern than an observation. The one thing that I think I alluded to before was that we're looking at ill-defined corneal haze in better than 50 percent of patients, if I recall.

The entry criteria were best corrected

visual acuity worse than 20/20 and progression, and of course, corneal haze in a patient who shows progression who's starting off with pretty poor vision is a bit different from corneal haze in somebody who's starting off with relatively better vision.

Unfortunately, the haze or corneal opacity, as described, was again very poorly defined. So unfortunately, it makes it a little bit difficult to assess how significant that might be for patients entered into the study with better enrollment acuity.

In general, the effect of something like haze and opacity can be difficult to assess. We know this from our refractive surgery studies. And so in those particular cases where having better patient, subjective patient data would have been helpful -- and that may or may not be uncovered in a review of the data that has to do with subjective patient outcomes -- in reviewing those data it might be helpful to try to correlate that with the description, plus/minus of haze, and what the

patient's starting acuity was.

DR. AWDEH: Dr. Sugar?

DR. SUGAR: My memory is probably faulty, but I thought that beyond six months that did not persist. I don't know what slide to pull up. I think it's from the sponsor's data.

DR. AWDEH: Does the sponsor have a slide regarding corneal haze post six months?

DR. HERSH: The 12-month. So looking at ocular AEs at 12 months, as you see here, corneal haze remained in four subjects in the KC group, and there were two corneal scars in the ectasia group. So for the preponderance of patients, the haze cleared completely.

DR. AWDEH: So, Dr. McLeod, does this address what you're asking or not?

DR. McLEOD: I would certainly hope so. So you have a total of six patients who had some degree of corneal opacity.

DR. HERSH: That's right. Yes.

DR. McLEOD: So the 68 -- and that was your 3-month data, was it, 68 percent or something like

that?

DR. HERSH: That was our early data.

DR. McLEOD: Your three-month. One month? Show the original AE slide. Right. So this is the three-month data, yes. What we find is that the haze patients tend to be fairly consistent at the one-month follow-up and the three-month follow-up. Then there is a general dissipation where on average, it returns to baseline, and a few patients, as you see here, still retain a bit.

In just some sub-analyses, it does not appear. We could not correlate haze with end result of Kmax change or end result of visual acuity.

DR. AWDEH: Dr. Weiss?

DR. WEISS: Yes. Dr. Hersh, I had a question, so I understand it a little bit better. Table 47 had a summary of ocular diverse events. Corneal opacities, there were initially 147 that were resolved. But it says ongoing were 31. And this is from the advisory committee briefing package.

So why were there 31 ongoing corneal opacities?

DR. HERSH: This is table 41 in the briefing document -- sorry, table 47 in the briefing document.

DR. WEISS: And it's on page 135.

DR. HERSH: If you could just clarify what time point this is at? Okay. So these are AEs that are observed at any time point. So -- one second.

(Pause.)

MS. NELSON: So what you're seeing here is cumulative numbers in terms of what was seen from baseline to month 12 in any eye, any cross-link-treated eye, at any time in greater than or equal to 2 percent. So keep in mind that's just the greater than or equal to 2 percent, any cross-linked eye, baseline to month 12, at any time.

DR. WEISS: Just so I understand the ongoing, the ongoing which is 31, those didn't resolve? At the end of the day, do you only have four eyes that have the haze, which is the four

eyes that you showed in the other slide? Or are there more because there might be some that weren't followed out to 12 months, and a six months' time they had it and then they disappeared from the study?

DR. HERSH: Right. I believe what you said second is correct. They could have been followed and then disappeared from the study, yes.

DR. WEISS: This is Jane Weiss again. So then that would create more of a concern, I think, because if we believe there's only four eyes, then we can say among all the patients treated, corneal opacity wasn't a major problem.

But if we believe there's perhaps 31 eyes and they weren't captured in the four because some of these were lost to follow-up or didn't come back, then it may be more of a problem. And I don't really believe it's that large a problem, so I'm asking you to help me --

DR. HERSH: In fact -- excuse me. I'm sorry. In fact, we have to go back, I think, and define exactly what this is. But this may comprise

a number of the patients in 001, where the study was discontinued early and a number of patients were lost to follow-up before completion of the 12-month time frame. We need to check that. But that's a seemingly plausible explanation for it.

DR. WEISS: So from your experience with this, is it possible that it's not infrequent for a patient to have haze initially, but in the vast majority it goes away? That's what I need some help with.

DR. HERSH: Yes. We looked into our own patient population, and typically, patients virtually all develop some of this cross-linking-related corneal haze. And this is from that paper, and it was judged by Scheimpflug densitometry.

The corneal haze tends to look somewhat like the clinical picture that we see here. As time goes on, it evolves into what people have described as the demarcation line, which is a granular, midstromal haze. You can see occurs and plateaus at one month and three months, and it dissipates to billion.

So there was no significant difference in haze, looking at the population preoperatively and postoperatively. But as we see with the four, five, six patients that remain, there are some patients that still have some haze at the end of the 12-month follow-up time course. And when we looked at these patients, we could not find any significant clinical sequelae that we could relate to the haze when we analyzed those patients.

DR. AWDEH: Are there any other comments regarding haze?? Are there any other comments -- is this regarding haze?

DR. JENG: It is. This Bennie Jeng. Sorry.

DR. AWDEH: Good. Dr. Jeng?

DR. JENG: Sorry. I tried to understand. I still don't understand what ongoing means because that's at any time point that they've had it, and it's just not very clear to me.

MS. NELSON: Right. So ongoing means that it could have occurred at any time, not necessarily that it had been ongoing from baseline, that it could have occurred at any time in any eye in

greater than or equal to 2 percent between baseline and month 12.

DR. AWDEH: So just to restate what you said, the 10 percent number that we just saw on table 47 that says ongoing means that they could have had haze at any point during the trial. It could have resolved.

DR. NELSON: Correct.

DR. AWDEH: And they still would have been counted as ongoing on that table?

DR. NELSON: Correct.

DR. WEISS: So how do you differentiate between the resolved corneal opacity group versus the ongoing corneal opacity group?

DR. HUANG: This is Andrew Huang. I think the more reasonable explanation is that this is the cumulative incidence. So you have 187 incidents of post-treatment corneal opacity. But the so-called ongoing is really between the visit.

For example, on visit, postoperative visit one, you have a haze, on postoperative visit two, you have a haze, that's the ongoing. But then on

visit three, this patient could have disappear. So the ongoing visit were going down.

But on the other patient, they may not have a visit one and they may have a visit two, become have a haze, and on visit three has a haze, visit four, has a haze. So that become ongoing. So the cumulative ongoing is always less than the total haze. And so at the end, after a year, it's only four left. So basically, it's the net difference of the cumulative incidence.

DR. HERSH: Right. That's the proper explanation. Thank you.

DR. AWDEH: Dr. Eydelman?

DR. EYDELMAN: Not as a follow-up but in light of all the comments that I just heard, I was wondering if we can project back sponsor's slide 76. Even though it's on the slide, I think perhaps there was some confusion I heard.

The 293 is the number of eyes available from baseline to month 12. That's not the number of eyes available at 12 months post-treatment.

In other words, for sham eye, sham eye could

have been treated at six months. And they were still available at month 12, so right here they would be captured as part of the 12-month safety cohort. However, they were only six months after -- well, perhaps we can have the sponsor to clarify what this means.

DR. HERSH: All right. All of these eyes were treated eyes that completed 12-month follow-up after their treatment.

DR. EYDELMAN: Thank you. That's not --

DR. AWDEH: So I think there's still some confusion on this topic. I think what the panel is asking for is what are the number of eyes at month 12 that have opacity or haze?

DR. HERSH: Could you repeat that question one more time, please?

DR. AWDEH: So what the panel is asking for: What are the number of patients at month 12 that had either corneal opacity or haze?

DR. HERSH: Oh, that, if we look at the last slide. So at month 12, there were four subjects with KC that had haze, two subjects with KC that

had a corneal scar in ectasia. There were four subjects -- I'm sorry. There were two subjects that had a corneal scar. So this was the incidence at the one-year time point.

DR. AWDEH: And just for clarity, can you indicate the N for the progressive keratoconus group and the N for the corneal ectasia group?

DR. HERSH: They are, as we saw in the last slide, 293 in the keratoconus group and 219 in the ectasia group. So all eyes that were treated.

DR. AWDEH: Is the panel satisfied with the current slide and the current answer? Dr. Sugar?

DR. SUGAR: A question. Is that LOCF?

DR. HERSH: No. That's real, observed data. So these are patients who came in and were observed for their 12-month visit who had cross-linking and all AEs were captured at that point.

DR. AWDEH: Dr. MacRae?

DR. MacRAE: Yes. In that group, if you can put it up again, do we know whether they lost two lines of best corrected vision, or is there any other information in terms of that haze to give us

some feeling as to the degree of morbidity?

DR. HERSH: We could find you the exact data on those patients. I can tell you that in my cohort of patients, there was not a clinical sequelae of the corneal haze. So those patients in particular, we can find out exactly what it is for those four subjects. But in general, they did not have a decrease in vision.

DR. MacRAE: So the four haze eyes didn't have a decrease in vision?

DR. HERSH: Right. That's what I recollect from my own individual experience. But we can find out for those four patients exactly.

DR. MacRAE: Along the same path in terms of the corneal ectasia, that you had visual acuity reduced in four subjects, it would be helpful to know exactly how many lines of vision they lost.

DR. HERSH: Yes. When we looked at the patients who lost three lines or more in one of the previous slides, we couldn't find any specific preoperative characteristic that led to that. But we could also find out how much vision they lose.

DR. MacRAE: All right. Thanks.

DR. AWDEH: All right. Thank you.

Discussion question number 8: The applicant proposes indication of progressive keratoconus. Please discuss applicability of extrapolation to general keratoconus population. Dr. Sugar?

DR. SUGAR: I wasn't raising my hand. But it wasn't studied so we don't have data to apply to that question.

DR. AWDEH: Dr. Belin?

DR. BELIN: I'll take a different approach. I don't think they defined progressive keratoconus very well, so I would be more inclined to just use a general term, keratoconus.

DR. AWDEH: Are there any other comments on this topic? Dr. McLeod?

DR. McLEOD: The intent of the study was progressive keratoconus. It may be ill-defined, but that's the study. And in theory, it becomes a very different question to apply to a very different population, which is basically topographic change without advancement. I think

the applicant's proposal is irrational one based on the study.

DR. AWDEH: Thank you.

Does anyone on the panel have a comment regarding this question? If not, let's move forward. Dr. MacRae?

DR. MacRAE: I just have a comment. In terms of the literature, most of these studies have been based on progressive keratoconus. So I'd stick with the progressive keratoconus indication.

DR. AWDEH: Thank you.

That concludes the discussion portion. We're going to take a five-minute break while the voting system, the electronic voting system, gets up and running, and we'll resume in five minutes. Three minutes. Three minutes. So just stay in your seat. Let's stay right around here, please. Thank you.

(Whereupon, a recess was taken.)

DR. AWDEH: We're going to resume now. Please take your seats.

We will be using an electronic voting system

for this meeting. Once we begin the vote, the buttons will start flashing in front of each panel member and will continue to flash even after you've entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record.

We will then go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

So I will read the first question to the committee, if we can put it up on the screen, please.

DR. LEGUIRE: I believe I get to talk before people start the voting, given the consumer representative. Is that correct?

DR. AWDEH: Go ahead. Yes. We're getting there. Hold on one second. Let me read the question first.

The first voting question is: Has substantial evidence of efficacy and safety been demonstrated for the drug-device combination of Photrexa Viscous and Photrexa, riboflavin ophthalmic solution, and the KXL System, ultraviolet light, to support approval for progressive keratoconus? Yes or no?

Are there any questions or comments regarding the wording of the question?

(No response.)

DR. AWDEH: Before we proceed to a vote, I would like to ask our nonvoting members, Dr. Larry Leguire, our customer representative, Mr. Michael Pfleger and Dr. Gavin Corcoran, our industry representatives, if they have any additional comments at this time.

DR. LEGUIRE: Thank you. Larry Leguire here. First I'd like to recognize the advocacy groups for patients that have suffered vision loss due to LASIK surgery. I do share a lot of your concerns.

At the same time, this is an orphan drug-device used to treat complications of LASIK surgery and as well as patients that have not had LASIK surgery, i.e. those with keratoconus. It is important, I think, for everybody to recognize these are not normal eyes. These are patients that have a potentially blinding eye disease. And this is the first therapy in the United States that may provide these patients with some help.

Looking at this data as a researcher for 40 years, I see significant results. In terms of UV-A, I think there is progressive nature of the vision loss here. I think, overall, the side effects are tolerable and acceptable, given the therapy, and most of them were actually due to the therapy. And I also believe that there is an equivalency between the KXL and the UV-X devices.

In terms of patient satisfaction, we weren't given anything about that. But I just keep coming back to the fact that almost every patient in the study crossed over. That tells me that the patients were satisfied with the outcomes and satisfied with the surgery; otherwise, they simply would not have crossed over. So that's it.

DR. AWDEH: Thank you. Dr. Corcoran?

DR. CORCORAN: Yes. The only couple of comments that I have to make is -- one is around the study data, and to ask everybody to take a look at the weight of evidence. Not the tidiest studies; we've kind of dissected the data. Not the tidiest studies.

However, I think that it's important, looking at the patient need, the unmet medical need, and the data that's available, and so that in fact is there sufficient data to show that this would be useful to patients. However, we circumscribe that -- did we really look at the weight of evidence rather than just the specifics of each of the studies, rather look at it all

together. So thanks.

DR. AWDEH: Thank you.

Mr. Pfleger?

MR. PFLEGER: Yes. Just to carry on, on top of that, just a thank you to the sponsor. This is clearly in the area of unmet medical need, and it's appreciated that someone was willing to take on studies that they were not involved in originally and didn't design. So when you acquire these sorts of things, you live with the good and the bad. It's appreciated, though, that they were willing to do this in this area.

DR. AWDEH: Thank you.

If there's no further discussion, we'll now begin the voting process.

DR. HUANG: Can I ask a request? Is it possible for FDA or the sponsor to put up the labeling indications? Because we don't know how to answer the subsequent question.

DR. AWDEH: Yes. Could we pull up the labeling indications, please? Let's focus on question 1, and Dr. Huang, we will present those to

you. They should be in your data packet in front of you as well. Dr. Huang, the slide's pulled up for you.

Can we go to question number 1 again, please, voting question number 1? Thank you. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote, starting now.

Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. AWDEH: Everyone has voted. The vote is now complete. Now that the vote is complete, we'll go around the table --

DR. CHOI: For the record, we have 10 yes, 4 no, and 1 abstention.

DR. AWDEH: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, state their vote, and if

you want to, state the reason why you voted as you did into the record. We'll start at the first voting person on this side, which is Dr. Sugar.

DR. SUGAR: I voted yes despite the less than ideal protocol and data. I think that this study has demonstrated efficacy and safety and meets a clinical need.

DR. AWDEH: Dr. Matson?

MR. MATSON: Tracy Matson. I'm the patient representative. As a keratoconus patient, I'm satisfied with the safety and efficacy of the product, and I think it will be an important treatment option for patients everywhere.

DR. AWDEH: Dr. Belin?

DR. BELIN: I voted no. I would actually hope that the FDA would approve cross-linking based on the available data, and to approve riboflavin and UV to any manufacturer that uses good manufacturing practices.

But just based on this study, I think it was a poorly-done study, and I don't understand why, when they took over the data five years ago and

they realized it was poor, they didn't do an additional arm to validate the data.

DR. EVANS: I voted no.

DR. AWDEH: Say your name first, please.

DR. EVANS: Scott Evans. I voted no. I think the devil's in the details about how you ask this question. You asked whether its safety and efficacy have been demonstrated. That's a different question from whether you think it works or whether you think there's a medical need and so forth. And there are clearly a lot of issues in terms of design, conduct, and analysis of this trial, some of them fairly major. And I think we need better data.

DR. BROWN: Jeremiah Brown. I voted yes. I think the preponderance of the data showed a treatment effect and that the treatment was safe. My particular protocol issue, allowing patients to cross over, was very frustrating. But I think that overall, based on the natural history that we know of this disease, probably it was okay in terms of being able to evaluate the data. So I voted yes.

DR. McLEOD: Stephen McLeod. I voted yes. The study design and execution really required some very creative acrobatics to get this to the point where one could vote in the affirmative. Nevertheless, based on that and prevailing need, my vote has to be yes.

DR. FEMAN: I'm Steve Feman. I voted no. The biggest problem is that they have no patient treated with the machinery that they're trying to get approved, and we don't know if there are some subtle differences in the machinery design compared to the one in which the study was done that may make a difference. Essentially, in the study they've not shown that the treatment is better than just the riboflavin alone.

DR. AWDEH: Richard Awdeh. I voted yes.

DR. WEISS: Jane Weiss. I voted yes. I had many concerns with the study, but there is medical need.

DR. YOO: Dave Yoo. I voted yes. I pretty much agree with everyone else that there is a need. Not the best study, but I think enough data once

you ferret everything else out.

DR. OLIVIER: Mildred Olivier. I voted yes. There were a lot of problems and issues, of which I think also checking intraocular pressures on a regular basis. But I think there is a need for the population.

DR. JENG: Bennie Jeng. I think the data is not very clean, but I think it's convincing enough and there definitely is a medical need. I am very troubled by the getting approval for a machine, albeit similar, that is not the same. And there are nuances that could be different about it and could affect the efficacy. And that troubles me a lot, to approve a machine that has not been tested. We don't see any data.

But I had to balance that with the fact that there is a medical need, and the existing data with what they did was good. So I abstained because I was torn.

DR. MacRAE: Scott MacRae. I voted yes. As stated, the data was very messy and lots of patching, and it was disappointing that the

crossover was allowed at three months. I was wondering what the rush was.

When you look at it in a big picture retrospectively, if you've looked at that data at six months, if we had a crossover at six months, I think this would have been a lot easier to do.

But looking carefully at the literature and looking at this data, they're very similar in terms of the trends. And there was a very good study out of Australia that's very similar to this that follows out to three years, and that study is very convincing. It uses the same Dresden protocol, and it was very well designed, with a sample size of 49 for each group.

So are we supposed to give caveats in terms of what we would like, or are we going --

DR. AWDEH: Sure.

DR. MacRAE: Yes. So the one thing I would recommend is that in terms of treatment, I would recommend for progressive keratoconus and progressive ectasia until we get further information from the sponsor. Thank you.

DR. HUANG: This is Andrew Huang. I voted yes. Based on the data presented to me on the safety, I thinking it will be a safe treatment for the endothelial point of view for the patient. However, I'm not convinced with the efficacy.

Nonetheless, I believe this is novel technology. There is unmet medical need. We are really looking at a treatment probably efficacious in halting the disease progression. But so far, I haven't been convinced there will be a cure.

Nonetheless, I also would like to suggest maybe FDA or the sponsor maybe take into the meta-analysis of the existing literature to substitute the efficacy of the treatment.

DR. OWSLEY: This is Cynthia Owsley. I voted no. I was very moved by the comments from the patients during the public session, both the patients who have keratoconus and those patients who have problems post-LASIK.

I think these patients deserve evidence-based interventions, and the study was so methodologically flawed that I could not come to

the conclusion that it represented substantial evidence of efficacy.

DR. AWDEH: Thank you.

Let's move on to voting question number 2. If you could put the question on the screen.

DR. CHAMBERS: Are you going to come back to the other parts afterward, or which order are you going to -- I don't have a particular preference, but I recognize there are other parts if you voted yes.

DR. AWDEH: Sorry, sorry, sorry. Yes. Let's do that now. Yes. So sorry, let's go back to the voting question 1. There were three subsets of this. I'll read them.

If yes, recommend approval, do you have any suggestions regarding the draft labeling of the product? If the product is recommended for approval, are additional studies needed post-approval? If so, comment on the type of study : objectives, population, endpoint, duration, design.

Let's start with those two, and these two are addressed to the people that voted yes. Start

on this side of the table.

MR. MATSON: Tracy Matson. As patient rep, that's really not my area of expertise, so I don't have a comment on that.

DR. SUGAR: Joel Sugar. I don't think I have additional suggestions regarding the draft labeling, assuming that the labeling for physicians at least includes data on adverse events. In terms of section B, I think that the sponsor in their phase 4 covered this, and I agreed with their proposal.

DR. BROWN: Jeremiah Brown. I would like to see a statement on the label that says something about, the long-term effects and durability of this treatment are not known beyond 12 months, something like that.

DR. McLEOD: Nothing to add.

DR. WEISS: I agree with Huang, something in there about that there is no stability data. I would also like something in there to temper the visual acuity claims that may be made post-approval in terms of more accurately reflecting what

happened to vision, and also accurately reflecting the amount of flattening this does cause.

I also would ask the FDA to consider what was mentioned in the public hearing about having patients receive information about this, or I don't know if one could mandate that the patient receive the data, because my concern is, post-approval, this may be hyped into it can cure keratoconus, it can improve your vision, and all sorts of things.

It would be fair, I think, for the patient to have the objective data that, basically, the control group as well as the keratoconus group at various time points might have a small improvement of vision whether or not they were treated, and that the average flattening in this group was approximately 2.

DR. YOO: I have nothing else to add.

DR. OLIVIER: Nothing to add.

DR. JENG: Nothing to add.

DR. MacRAE: I already stated mine.

DR. HUANG: This is Andrew Huang. I'd like to see there is a restriction of the age because we

haven't been convinced that the pediatrics group is totally efficacious. And second, I also would like to see the restriction of the thickness.

There should be some range of the therapeutic range. I mean, the cornea have certain thickness and probably is a good indication. But however, if the cornea too thin, they may suffer from the endothelial toxicity even though we don't have the data. But I think there should be some sort of qualifying statement in terms of the range of the cornea thickness.

Also, I do concur that this should not be labeled as improvement of the vision. They can certainly indicate there might be a progressive effect. However, this is really just halting the progression, not the cure.

DR. AWDEH: Let's move on. For those of you who voted against the product for approval, if the product is not recommended for approval because additional studies are needed, please comment on the type of study or studies that are needed in your mind. Let's start with the noes on this side

of the table.

DR. EVANS: I would say this comment applies to whether it's a new study or even post-approval, to get the data you don't have, which --

DR. AWDEH: Could you state your name, please?

DR. EVANS: Scott Evans. I think it's important to get the data that you don't have. One of them you just mentioned, long-term data, I think would be helpful. More data on younger patients.

I would also begin to focus on clinical outcome data that represent functions of the patient. For some of this discussion, I was trying to figure out how relevant Kmax is in terms of clinical function. And of course, I want to know what's happening with the patients.

Lastly, given the paucity of comparative data, you've got to get longer-term control data as well.

DR. FEMAN: I'm Steve Feman. I voted no also. And I'd recommend them to repeat the study using the appropriate machinery. Do it like they

said they would.

DR. OWSLEY: Cynthia Owsley. I agree with Dr. Evans' comments. Looking back at your study, you received a lot of feedback about methodological challenges in that study, and it'll be in the record. And maybe you can learn from that for going forward. But also, in addition to what Dr. Evans mentioned, I would suggest beefing up recruitment and retention practices in the trials.

DR. AWDEH: Thank you. Moon has a comment before I move on to voting question number 2.

Dr. Eydelman, do you have a comment for us?

DR. EYDELMAN: No. Just in light of the comments made by several panel members, I just wanted to remind the panel one more time that the decision is to be based on the data presented and not on the potential data available in the literature on potentially different combination products.

DR. AWDEH: Dr. Weiss?

DR. WEISS: I would also like to add into the labeling for patients as well as physicians

that this machine wasn't used in the study, so they're aware of it.

DR. CHOI: For the record, Dr. Michael Belin is absent from voting for this question.

DR. AWDEH: Let's move on to question number 2. The question is on the screen. I'll read the question now.

Has substantial evidence of efficacy and safety been demonstrated for the drug-device combination of Photrexa Viscous and Photrexa, riboflavin ophthalmic solution, and the KXL System, ultraviolet light, to support approval for corneal ectasia following refractive surgery? Yes or no?

Are there any questions regarding the question?

(No response.)

DR. AWDEH: If there are no further questions, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection,

the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Vote taken.)

DR. AWDEH: Everyone has voted. The vote is now complete.

DR. CHOI: For the record, we have 6 yes, 4 no, 4 abstention, and zero no vote -- I'm sorry, 1 no vote.

DR. AWDEH: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, the reason that you voted as you did into the record. We're going to start with Dr. Feman.

DR. FEMAN: Thank you. I'm sorry, there's a cab waiting for me outside.

I voted no for the same reason I voted no on the earlier time, that no one has done the study using the device that's being planned to be used, and we have no data as to whether or not the device works appropriately with this medication.

DR. AWDEH: Thank you. Let's move to this side of the table and state your name, please, and your vote.

MR. MATSON: Tracy Matson. I voted yes, again for the same reasons as before, patient need.

DR. SUGAR: Joel Sugar. I voted yes, for again the same reasons as I stated for the last vote.

DR. EVANS: Scott Evans. I voted no, for basically the same reasons as already stated.

DR. BROWN: Jeremiah Brown. I voted yes. I wanted to acknowledge all of the public comments that were given and to let those who spoke know that we took their comments seriously and to heart. And my consideration in this case dealt with the overwhelming nature of the data despite the problems, that there was a biological effect, and that it was safe.

DR. McLEOD: I voted yes again on this one, based again on the preponderance of the evidence and the patient need.

DR. AWDEH: Richard Awdeh. I voted yes.

DR. WEISS: Jayne Weiss. I abstained on this one because of my concern of the lower numbers, not to demonstrate complete confidence in terms of knowing what the side effects might be in a large number as well as the other issues that have been previously raised. I also want to acknowledge the public comments.

DR. YOO: Dave Yoo. I chose to abstain on this as well. Similarly, I had issues with the numbers, and wanted to also acknowledge the patient comments. Thank you.

DR. OLIVIER: I abstained -- Mildred Olivier -- for the same issues that were raised earlier, and also because I was not sure preoperatively if some of those patients were clearly defined by diagnosis.

DR. JENG: Bennie Jeng. I abstained for the same reason. The data's not clean. The instrument being approved is not the one that was tested, but balanced against patient need, medical need.

DR. MacRAE: Scott MacRae. I voted yes, for basically the same reasons for the first vote.

DR. HUANG: I voted differently from the first question. I voted no. My major concern is that the corneal ectasia after the LASIK surgery is intrinsically a little bit different from the keratoconus.

Keratoconus tend to be paracentral, in the central location, so the current regimen probably is going to offer some effective treatment. However, most of the corneal ectasia that I have encountered, usually they are in the periphery, and then also that the cornea itself is really not well-centered and the topography itself may not totally represent the pathology.

So based on the technology and the small sample size, and also that the technology doesn't encompassing the larger area of the treatment, I voted no.

DR. OWSLEY: This is Cynthia Owsley. I voted no, for the same reasons I voted no in the previous vote.

DR. AWDEH: Could you put the question back up, please? I'm going to read the two sub-

questions for the yes group and then go around the table for those who voted yes.

If yes, recommend approval, do you have any suggestions regarding the draft labeling of the product? If the product is recommended for approval, are there additional studies needed post-approval? If so, please comment on the type of study: objectives, population, endpoints, duration, and design.

MR. MATSON: Tracy Matson. I have no recommendations, for the same reason as the last question.

DR. BROWN: Jeremiah Brown. The same labeling issue about long-term effects and durability not being known beyond 12 months. Also, in this group where the corneas may be thinner, probably should emphasize the importance of not proceeding if 400 micron thickness is not reached; there is a sentence in the label, but maybe another sentence explaining why that's important.

DR. McLEOD: Nothing to add.

DR. AWDEH: Dr. Weiss?

DR. WEISS: I would have the same labeling suggestions I had for the first question. But also, if no patients with radial keratotomy were included in the study, I don't think we should use the all-inclusive term refractive surgery and rather indicate the type of refractive surgeries that were actually studied, which I think were all laser-based.

DR. MacRAE: Scott MacRae. I voted yes, and I'd just include for progressive ectasia in terms of the labeling as a recommendation.

DR. HUANG: I recommend post-approval study. But it doesn't have to require a new study because this is a very bad. However, is a very unique study. The data submitted for review in four years after closure of the study, so you essentially have a built-in four years of results because the last enrollment was generally 2011, the completed data entry.

So as a result, we have four years of results that we don't even know. So especially in the so-called corneal ectasia after LASIK

population, I think that is a great opportunity to look into that set of data.

DR. AWDEH: Thank you.

For those who voted no, if the product is not recommended for approval because additional studies are needed, please comment on the types of studies that are needed.

DR. EVANS: Scott Evans. The same comments as before. Try to get the data you don't have -- younger folks, longer-term outcomes, and appropriate control data. And focus on functional outcomes for the patients.

DR. HUANG: Sorry. I jumped ahead.

DR. OWSLEY: I would just say everything I said before in relationship to the previous question.

DR. AWDEH: Thank you.

Before we adjourn, are there any last comments from the FDA?

DR. BOYD: Nothing except to thank everyone for their time.

DR. EYDELMAN: And I just wanted to extend

thanks to the teams, FDA teams, who have worked very hard to make this time deadline possible.

Adjournment

DR. AWDEH: We will now adjourn the meeting. Panel members, please take all personal belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the table on your way out. Thank everyone for their time today.

(Whereupon, at 5:24 p.m., the meeting was adjourned.)